MERIDIAN
MEDICAL TECHNOLOGIES™
A Pfizer Company

**Meridian Medical Technologies, Inc.** ™
1945 Craig Rd.
St. Louis, MO 63146

CONFIDENTIAL
April 14, 2017

Miguel A. Hernández
Director, Compliance Branch
United States Food and Drug Administration
8050 Marshall Drive, Suite 205
Lenexa, KS 66214

Re: Response to Food and Drug Administration (FDA) Form 483, Issued March 24, 2017, FEI Number 1950222

Dear Mr. Hernández,

This letter and the accompanying attachments respond to the Inspectional Observations in the Form FDA 483, issued to Meridian Medical Technologies, Inc. (hereafter "Meridian" or "MMT") following FDA's inspection at our St. Louis facility from February 20 – March 24, 2017.

Meridian and its parent company, Pfizer, Inc. (hereafter "Pfizer"), acknowledge the significance of these observations and recognize the importance of addressing them thoroughly and completely. We are committed to making improvements to our Quality System to make it and the corresponding subsystems more robust, while also ensuring our corrective actions meet the Agency's expectations and our own high standards. This response describes not only the actions we are implementing to address the specific issues identified in the 483, but those we are pursuing more globally to enhance related aspects of our Quality System.

**Commitment To Collaborate With FDA**

Patient safety and product quality remain Meridian and Pfizer's highest priorities. We are committed to an ongoing dialogue with the Agency and welcome FDA's feedback or suggestions as we move forward with our important work, as evidenced by our constructive discussions with FDA on the current recall of EpiPen lots potentially impacted by defective Power Pak

components, related to Observation #1. We will continue to keep FDA informed of our progress on the recall.

**Corporate Engagement**

Pfizer and MMT senior management understand the significance of items raised in the 483 and fully appreciate the need for a comprehensive response. Management from both the corporate and site level have been fully engaged in the preparation of this response and will provide oversight moving forward to help ensure that the enhancements made at the site are both effective and sustainable.

Management is also committing the necessary financial and personnel resources, including the use of independent outside consultants, to effectuate the improvements described in the attached Responses. Corporate management will continue to support the site, including the Quality Team, throughout the duration of the improvement process, recognizing that this is a long term commitment that will require sustained engagement and resources.

**Third Party Support and Expertise**

To assist us in implementing corrective and preventive actions at the facility, we will engage an experienced and reputable third party consultant that specializes in QSR remediation. The consultant will help us on several fronts:

- Partnering with us on our focused efforts to enhance our Design Control and Complaint Investigation programs, as described below
- Working with us to evaluate our AQLs
- Working with us to develop a Compliance Action Plan to ensure a holistic response to the 483 Observations
- Performing CAPA Effectiveness Checks to help us gauge progress and refine our efforts as appropriate

As issues emerge in our enhancement activities on other subsystems, we may also enlist additional third party support as appropriate.

**Compliance Action Plan**

Meridian is committed to a holistic response that addresses the discrete issues identified in the 483 as well as the broader GMP subsystems implicated by the Observations. To that end, we will work with our outside consultants to develop a Compliance Action Plan ("CAP") that will identify corrective and preventive actions beyond those described in this Response to enhance our systems and processes.

The attached Responses cover all of the issues identified in the 483, but as a result of our initial evaluation, we have identified three key areas for improvement that will be the primary focus of our CAP:

> **Design Controls**: MMT and Pfizer first began to manufacture the current suite of products before FDA issued its 2013 Current Good Manufacturing Practice Requirements

for Combination Products. Accordingly, the site's GMP quality system historically has been focused on compliance with the GMP requirements in 21 CFR Part 211 consistent with the product registrations as drugs. In recognition of the evolving regulatory standards applicable to approved drug and device combination products, the site has enhanced its device quality system in recent years in accordance with QSR-specific requirements in 21 CFR Part 820, by developing procedures on design control and design transfer.

As indicated by the Observations in the 483, expectations for the design components have evolved, with enhanced expectations for the design features for products that have previously been approved by FDA under the New Drug Application process. In response to these Observations, we have committed to update our procedures on Design Input, Design Output, Design Verification, and Design Validation. We are also working on a related Risk Assessment. As part of this effort, we are engaging a third party consultant to help us to evaluate our Design Control practices and recommend enhancements. Their assessment will consist of document reviews, evaluation of our design history files and device master records, and review of our procedures and day-to-day practices. The consultant will also focus on design transfer, design verification, and design validation practices. All of their work will be captured in the CAP.

**Complaint Investigations**: Since the inspection, we have taken several steps to improve our complaint investigation process, including modification of our procedures on Complaint Handling and Notification to Management. In the attached Responses, we have also committed to analyzing historical trend data on all complaints and establishing new action limits. To supplement these efforts, we will ask our third party consultant to audit our complaint investigation and trending practices and to help us identify opportunities for improvement that augment the commitments made in these Responses. The consultant's audit, and the actions we take in response, will be included in the CAP and described in future updates.

**AQLs**: Since the inspection, we have committed to changing our AQLs to (b) (4) for critical defects, as well as updating our defect classifications. We will also ask the third party consultant to help us evaluate our AQLs and mean complaint alert limits across product lines to assure we are appropriately calibrating risk in accordance with FDA regulation and guidance and industry standards. Based on their feedback, we will take additional action as necessary to be sure our standards and alert limits align with best practices.

All of the commitments made in the attached Response will be included as part of the Action Plan, and they will be augmented over the next few weeks as we identify additional opportunities for improvements. The CAP is an iterative document; as new commitments arise from the gap analyses and reviews promised in these Responses, those commitments will be integrated into the CAP to ensure complete transparency and accountability. The CAP will identify timeframes for completion of commitments, and it will also include clear goals and deadlines. We expect to have the CAP drafted by June 15, 2017 and will share it with the Agency as part of our first update in July as noted below.

**Update to Responses**

We will provide updates to FDA on a quarterly basis, or more frequently if requested, on the status of our progress with respect to the 483 responses and CAP. Our first quarterly update, for the quarter ending June 30, will be submitted on or before July 30, 2017. This first update will also include a copy of our CAP. If you have any questions or concerns about this Response in the meantime, please do not hesitate to contact us.

Please note that this letter and the 483 responses contain confidential information related to MMT's business operations and processes and accordingly are not subject to disclosure under the Freedom of Information Act, 5 USC 552(b)(4) and 21 C.F.R 20.61(a)-(b).

Sincerely,

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cc: Cheryl Bigham
District Director, Kansas City District Office

**OBSERVATION 1**

*There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. Specifically,*

**OBSERVATION 1A**

*Your investigation of two complaints of 'Failure to Activate' for the EpiPen 0.3 mg Auto-injector finished product lot number 5FA665 did not extend to all potentially impacted lots. Your firm confirmed these complaints through investigations conducted under QAR Detail #PR ID: 22268 opened 5/9/l 6 and QAR Detail #PR ID: 28587 opened 2/23/17. These investigations identified manufacturing defects that resulted in distorted* (b) (4) *in the Power Pak* (b) (4) *of the Power Pak assembly. This assembly is used in both EpiPen and EpiPen Jr. Auto-injectors. Power Pak assembly lots* (b) (4) *and* (b) (4) *were identified as potentially affected lots that were included in finished product lots. Your firm inspected all Power Pak* (b) (4) *for defects that were part of Power Pak assembly lots* (b) (4) *. Your investigation implicated* (b) (4) *additional Power Pak assembly lots that were not utilized in finished product,* (b) (4) *. You inspected lot* (b) (4) *and found up to 11 instances of flash near the* (b) (4) *and rejected this lot. Lot* (b) (4) *was also rejected but you did not evaluate or inspect the lot to determine if additional* (b) (4) *manufacturing defects were present. Your firm did not implement an inspection of complaint devices alleging similar failure modes for "failure to activate" / "difficult to activate" to determine if these devices had a distorted* (b) (4) *From your investigation,* (b) (4) *finished product lots remain on the market that contain potentially defective Power Pak* (b) (4)

**Response to Observation 1A**

Meridian Medical Technologies, Inc. (MMT) and Pfizer senior management understand the significance of the items raised in Observation 1A and recognize that robust root cause and product impact analyses are essential features of a strong Quality System. In response to this Observation, MMT and Pfizer have taken several short and long term actions with three critical goals in mind: (1) assuring the safety of product in the field; (2) identifying the scope of the issue and the procedural gaps that allowed for it; and (3) developing procedural solutions to help ensure the issues do not recur in the future. These actions are set forth below, followed by a description of MMT's investigation into the complaints received and corrective and preventive actions to address (b) (4) defects at the component supplier.

First, to address the issues from a systemic standpoint, SOP-QLA-MQA-00004, *Notification to Management*, is being updated to ensure that formal notification to management occurs for any out of specification (OOS) result, whether it is for a finished product, in-process sample, or incoming component. When a lot of incoming component fails to meet a specification, the investigation will include full lot traceability for the components and respective sub-components used in MMT products to help connect the risks in one lot to potential issues in others. A

Notification to Management (NTM) will be issued for all incoming rejected component lots and include an analysis, based on lot traceability, of all lots and marketed product that could be potentially implicated. This NTM will help assure that potential market impact is assessed and properly scoped from the outset. It will also help ensure the assessment considers potential impact on all products within scope. MMT recognizes that a key Agency concern is that the site did not adequately evaluate product complaints in conjunction with the lots it had rejected for critical defects several months before. The enhanced procedure will facilitate those connections and ensure management involvement early in the process. The updated NTM procedure will be implemented by 31MAY2017.

Second, MMT has also enhanced Job Aid JA-DVL-PDV-10803 to specify that product complaint samples associated with (b) (4) must, be disassembled as part of the root cause analysis. This is true regardless of the condition of the sample received or content of the (b) (4). MMT's past practice was to perform (b) (4) testing in a laboratory on Failure to Activate complaint samples that were in a non-activated state and then disassemble and inspect the complaint samples that failed to activate normally. Additionally, MMT disassembled and inspected Failure to Activate complaint samples where the complaint narrative indicated a difficulty with activation (i.e. multiple unsuccessful attempts followed by successful activation). This process is how both confirmed complaints for lot 5FA665 were handled at the site. In the recent past, the site did not always disassemble samples that had been in fact activated when associated with a "Failure to Activate" complaint. As of 28FEB2017, all such samples have been subject to (b) (4), which includes an (b) (4).

Third, as discussed with the FDA inspection team during the inspection, MMT reopened the investigation in February and conducted a retrospective review in which the site disassembled all complaint samples that were on hand at the time of the inspection and that were associated with Failure to Activate complaints, and found no defective (b) (4).

Fourth, as described below, MMT has fully reviewed the investigation for the defective Power Pak (b) (4) component and conducted a thorough Product Impact Assessment. The Product Impact Assessment concluded there is very little risk that defective product is in the field. Out of an abundance of caution, however, MMT has recommended market action for (b) (4) finished goods lots that remain on the market due to related lots of Power Pak (b) (4) components. That process is now underway, and MMT has engaged the recall coordinator at the Kansas City District Office.

Additionally, the supplier of the assemblies, (b) (4)), has implemented the following corrective actions based on MMT's extensive engagement with them on root cause:

- As of May 2016, (b) (4) of all Power Pak (b) (4) was instituted for all on-going (b) (4) production.
- As of May 2016, (b) (4) inspected all inventories of Power Pak (b) (4) for deformed (b) (4).

- As of July 2016, (b) (4) have been added to (b) (4) to eliminate any (b) (4).
- As of October 2016, (b) (4) has updated their procedure to require a product impact and frequency for Risk Assessment.
- As of April 2017, (b) (4) had redesigned the (b) (4) to include (b) (4) allowing them to be (b) (4)
- Output will be tied to the (b) (4) system as a (b) (4)
- (b) (4) is targeting the same corrective and preventive action (CAPA) for the (b) (4) for May 2017.

On 11APR2017 (b) (4) notified MMT that they had identified an abnormal (b) (4) in upstream production as part of its enhanced 100% visual inspection process. MMT contacted FDA's recall coordinator on 14APR2017 regarding this new information. (b) (4) is currently evaluating the nature and cause of the issue, and all Power Pak assembly work using Power Pak (b) (4)) has been postponed pending the completion of the investigation. Quality and technical colleagues from MMT are currently on site at (b) (4) assisting with the investigation.

Background: Complaint and Field Alert Report Summary

The initial complaint report associated with EpiPen lot 5FA665, complaint number 2016-04-0023613-US for a Failure to Activate, was received on 28APR2016. The complaint sample was received and confirmed by MMT on 09MAY2016. An initial FAR was filed by MMT for this event on 12MAY2016. The final NDA Field Alert Report (FAR) was filed on 03JUN2016, concluding that no market action would be taken due to the low level of the defect as demonstrated by routine and additional testing that was performed (and which is described below in more detail).

A second complaint report associated with EpiPen lot 5FA665 (complaint number 2016-12-0074161-US) was received at MMT on 20DEC2016 from Mylan. The complaint was designated as "Injector, Difficult to Activate," and an initial FAR was filed on 23DEC2016 before the sample was received, as it was the second complaint for EpiPen lot 5FA665. The final NDA Field Alert was filed on 16FEB2017, concluding that no market action would be taken, since the complaint sample did fire and required (b) (4) was only at the major defect level and not at the critical defect level of "did not activate".

Following discussions with FDA, both of the NDA Field Alerts were reopened on 15MAR2017 to document follow-ups and a change in the market action decision for 5FA665. Based on the investigational findings of root cause, the extensive testing and inspection of the Power Paks, and a historical review of complaint data, MMT concluded that, while the (b) (4) could necessitate the use of additional force to activate, it would be a rare event for the defect to lead to a Failure to Activate.

Still, out of an abundance of caution, on 28MAR2017 MMT made the decision to recall the lots in the scope of the investigation that contain a Power Pak (b) (4) from the relevant lots. This decision was communicated to FDA on 29MAR2017 and the FDA supported this recommendation.

Background: EpiPen Auto-injector

The EpiPen injector is activated by mechanical means of the patient removing the safe pin and pushing the auto-injector against the thigh, which applies force to the nose of the injector. When force is applied to the nose of the injector (b) (4) activate the injector and deliver drug through the needle. A deformed (b) (4) can result in difficulty or inability for the injector to properly (b) (4) under appropriate force applied to the nose of the injector.

The functional components of the Power Pak, including the Power Pak (b) (4) with (b) (4) are produced and assembled by a third party supplier, (b) (4), and are received by MMT as a complete sub-assembly. The plastic components of the Power Pak including the (b) (4) are (b) (4) and assembled into the Power Pak assembly by this supplier. Power Pak (b) (4) Each (b) (4). Each (b) (4) produces (b) (4) which contains a (b) (4) During the (b) (4) are (b) (4) per the specification. Once acceptable parts are obtained and (b) (4) production is diverted to the acceptable product bin. (b) (4)

**The Lot Rejection and The Complaints**

Power Pak Incoming Test Failure

On 01FEB2016, one Power Pak unit from MMT lot (b) (4) (Vendor lot (b) (4)) failed an incoming test at MMT: One of the units failed to fire when an (b) (4). was applied. This Power Pak lot was rejected and a supplier investigation was requested.

Initial supplier feedback indicated that the defect was isolated to the (b) (4) incoming Power Pak lots received at that time, so both lots were rejected ((b) (4)) and not used in any EpiPen production. Lot (b) (4) was returned to (b) (4). After they were disassembled, however, (b) (4) discovered 11 instances of minor flash in the (b) (4) area.

In the Observation, the Investigators note that (b) (4) thoroughly evaluated the defects in lot (b) (4), finding up to 11 instances of flash near the (b) (4), but MMT did not conduct a similar evaluation of lot (b) (4) before rejecting it. There were two primary reasons for this. First, based on the review of lot (b) (4) and discussions with the supplier, MMT had a fairly well characterized understanding of the problem when it rejected that lot. Second, the supplier advised us that (b) (4) used a common lot of (b) (4) as used in lot (b) (4), so we had resolved to in an abundance of caution reject the latter lot on that basis

alone, despite the fact it passed our acceptance inspection criteria. Accordingly, the site did not see a compelling reason to proceed with further testing.

Initial Complaint Sample and Investigation

The initial complaint sample for an un-activated auto-injector for lot 5FA665 (complaint number 2016-04-0023613-US) was received on 09MAY2016 and evaluated by MMT on 09MAY2016. The analysis concluded the carrier tube and cap were present and intact. The safe pin was present and showed no anomalies. The needle cover was in the pre-fire state (retracted) and the Power Pak was in the pre-fire state. The plunger was not visible through the window and was in the normal position for an un-activated auto-injector. The needle sheath was visible through the needle cover hole. An attempt was made to hand fire the auto-injector; however, the unit did not activate. The label was removed from the auto-injector and the sample was disassembled and the auto-injector components were visually inspected, and present. The (b) (4) and Power Pak (b) (4) did not have visible defects. However, the review of the Power Pak (b) (4) revealed that the (b) (4) was severely deformed.

Of the Power Paks used in lot 5FA665 (b) (4) were from lot (b) (4) lot (b) (4) ) and [redacted]% were from Power Pak lot (b) (4) lot (b) (4) ). (b) (4) Power Pak lot (b) (4) used (b) (4) lots of Power Pak (b) (4) ). The (b) (4) lots associated with Power Pak lot (b) (4) and (b) (4) lot (b) (4) were made at the (b) (4) on a (b) (4) (as opposed to the (b) (4) at issue here), which was determined by the supplier investigation (described below) to not be in scope. Based on the supplier's use of the impacted Power Pak (b) (4) lot (b) (4) to assemble multiple Power Pak lots and the corresponding usage of these Power Pak lots in multiple EpiPen finished good lots, the following EpiPen finished good lots were identified as being in scope and potentially impacted: 5GR765, 5GN767, 5GK771, 5ED824, 5GM631, 5GM640, 5FA665, 5GU763, and 5GN773.

An internal quality notification report, (QNR) # 2016-116, was initiated at MMT due to the results of the complaint sample evaluation. Based on the results of this evaluation (confirmed defect), the FDA was notified of the first discovered defective unit in the field via an initial NDA Field Alert submitted to the FDA Kansas District Office on 12MAY2016. On 03JUN2016, the final NDA Field Alert for this confirmed complaint was filed by MMT. No market action was recommended due to the low level of the defect as determined by the investigation at the supplier and the routine and additional testing that was performed by MMT, the sequence of which is described below:

First (b) (4) MMT colleagues visited the (b) (4) manufacturing site on 11MAY2016 to support the investigation into the deformed (b) (4) found on the finished drug product unit in the field. The investigation determined that the deformed feature in the Power Pak (b) (4) of the returned auto-injector was due to a (b) (4) during processing. The returned auto-injector was found to have a Power Pak (b) (4) produced from the (b) (4) , based on the (b) (4) . (b) (4) have (b) (4) along with the (b) (4) . The returned auto-injector sample was (b) (4) . The Power Pak (b) (4) have a (b) (4) that (b) (4) and

allows (b) (4). The (b) (4) is (b) (4) in which (b) (4) called a (b) (4)

Second, (b) (4) ran engineering studies to replicate the defective part and confirm the (b) (4) This was done by (b) (4) to the (b) (4) in the (b) (4) during an engineering study run. After several cycles of the (b) (4), the defect was created. When the (b) (4) initiated the defect was not seen. This same engineering study was performed with the (b) (4), and it was determined that this issue did not exist in the (b) (4). Based on the study results and the identification of the source of the deformed Power Pak, lots containing (b) (4) were then removed from the scope of the investigation.

Third, the cause of the (b) (4) was believed to be due to an isolated event where a (b) (4), subsequently remedied itself, and the (b) (4). A (b) (4) would have been detected in the (b) (4). No defects were detected in the (b) (4) testing, which are (b) (4), indicating that the (b) (4) was temporary.

Fourth, the results of the following routine testing by both MMT and (b) (4) showed no defects in the potentially impacted lots released by MMT:

- In-process sampling/inspection of (b) (4) during manufacturing. Zero defects out of a sample size of approximately (b) (4) lot.
- MMT and (b) (4) each tested approximately (b) (4) Power Paks (b) (4) per lot) for (b) (4) from February 2011 to February 2017 with just the single failure discussed above for (b) (4) lot (b) (4).

Fifth, in order to verify the conclusion that this was an isolated event, additional sampling and inspection of other lots of inventory and reserve samples was performed. A total of (b) (4) Power Pak (b) (4) were inspected by (b) (4), and no defects were found. MMT disassembled and inspected all complaint samples on hand for Failure to Activate, and found zero defective (b) (4). Finally, MMT disassembled and inspected reserve samples from (b) (4) different EpiPen lots (a total of (b) (4) samples across (b) (4) lots) and found zero defective (b) (4).

<u>Follow-up to Initial Complaint Investigation – Review of Lot Associated with Power Pak Incoming Test Failure</u>

During a final review of (b) (4) batch records performed by MMT on 26JUL2016 to close the investigation for the failed incoming Power Pak lot (b) (4), an additional Power Pak (b) (4) lot (b) (4) was identified as being used to manufacture Power Pak lot (b) (4). A new QAR was initiated based on this finding (PR23913). As a result, the following EpiPen lots were added to the scope of the investigation: 6GM072, 6GM082, 6FA293, 6GN215, 6ED117, 6GM088, 6FA292, 6GM087, 6GM198, 6GM081, 6GM091, 6GM199, and 6GH294.

<u>Second Complaint Investigation</u>

The second complaint report was received for EpiPen 0.3 mg lot 5FA665 for Failure to Activate, and an NDA Field Alert was filed on 23DEC2016 prior to receiving the sample, since it was

from the same lot number that had a prior confirmed complaint. The complaint narrative indicated that a physician could not get the unit to activate, but then later the injector was activated. The complaint was that the "needle got stuck when firing". The complaint sample was received at MMT on 17JAN2017 for evaluation. Since the pen had been activated with force as reported, MMT disassembled and assessed the Power Pak for this product. The Power Pak within this complaint unit was found to activate at (b) (4) lbs. This activation force of (b) (4) lbs. would be classified as a major defect in a fully assembled EpiPen / EpiPen Jr. drug product unit. This activation force would also result in a Power Pak lot rejection if discovered upon incoming MMT Quality Control testing. The Power Pak for this complaint unit was disassembled to examine the Power Pak (b) (4). A slightly deformed (b) (4) was observed within the Power Pak (b) (4) for this complaint sample.

The final NDA Field Alert was filed on 16FEB2017, concluding that no market action would be taken, since the complaint sample did fire and required activation force was only at the major defect level and not at the critical defect level of "did not activate".

Follow Up Investigation at the Supplier

Based on the second confirmed complaint, a follow up investigation was performed at (b) (4) by Pfizer, MMT and (b) (4) to confirm root cause for the (b) (4) defect. A formal investigation was performed, which included a comprehensive root cause analysis, and concluded the root cause for the (b) (4) defect was again a (b) (4) may have been due to a temporary (b) (4).

MMT Testing During Incoming Inspection

Power Paks are received at MMT and entered into the inventory system under a unique lot control number. There is a unique lot control number for each unique supplier lot of approximately (b) (4) Power Paks. The incoming lots of Power Paks are sampled by MMT Quality Control for testing. (b) (4)) samples are tested from each Power Pak lot receipt for (b) (4) testing per the MMT Incoming QC Test Report. The activation firing force specification of "not to exceed an activation force of (b) (4) pounds" is a critical defect during incoming component inspection with no failing units allowed. An incoming test result has only occurred one time in the past ten years at this level (b) (4) lot (b) (4) - discussed earlier).

Summary:

In response to the issue, MMT has pursued a range of investigative actions under its Quality System to assure the safety of product in the field, identify the scope of the issue and the procedural gaps that allowed for it and develop procedural solutions to ensure the issues do not recur in the future.

First, MMT completed a product impact assessment, which included a retrospective complaint review, retrospective product review, and several product tests to substantiate that the creation of a defective (b) (4) in a Power Pak (b) (4) is an extremely rare occurrence. Still, out of an abundance of caution, on 28MAR2017, MMT made the decision to recall the goods in scope

of the investigation that contain Power Pak (b) (4) lot (b) (4) (confirmed complaint investigation for 5FA665) or Power Pak (b) (4) lot (b) (4) (potential cause of incoming Power Pak activation force investigation).

Second, MMT thoroughly investigated the nature and source of the issues here through its QAR system. To this end, MMT conducted an (b) (4) that involved review of procedures, product testing, an engineering study, and audits of the part supplier.

Finally, to address these concerns moving forward, MMT is implementing procedural enhancements as part of its CAPAs. These include updates to procedures on Notification to Management and Product Complaint Handling (refer to Response 3A). Collectively, these improvements will help ensure that concerns at issue here do not emerge as a future problem. These procedural enhancements will be in place by 31MAY2017.

**OBSERVATION 1B**

*Your firm did not perform* (b) (4) *testing" on the six (6) implicated lots identified in QAR PR 15815 prior to release of the lots. This QAR was opened when EpiPen Jr. lot 5GR446 failed functionality testing for low delivered volume due to* (b) (4) *defect. Your firm listed the most probable root cause of the* (b) (4) *defect as the presence of a non-homogeneous area in material. Your investigation for the other finished product using these* (b) (4) *was limited to batch record and testing record review. No additional physical tests were performed.*

**Response to Observation 1B**

MMT issued an Initial NDA FAR on 01JUL2015 for this functionality test failure. The root cause of the delivered volume failure was that a fractured portion of the (b) (4) shortly after activation, thus (b) (4) in 1 of the (b) (4) units tested per routine procedures for batch 5GR446. In the first follow-up NDA FAR issued on 29JUL2015, MMT communicated that supplemental physical (b) (4) testing of an additional (b) (4) units from within lot 5GR446 was performed. This supplemental testing included activating (b) (4) units and inspecting them for (b) (4) integrity. It should be noted that lot 5GR446 contained 100% of its (b) (4) from control lot (b) (4), while other finished good lots in-scope contained anywhere from (b) (4) % of their (b) (4) from lot (b) (4). No defects were discovered in the supplemental testing. The follow-up FAR explained that, even though the defect was assured to be low level, with a (b) (4) % confidence Unacceptable Quality Level (UQL) of (b) (4) % for defects of this nature within lot 5GR446, MMT had decided to reject lot 5GR446 for having a confirmed out of specification delivery volume result. This FAR also stated that the other finished good lots that included (b) (4) from the same lot would be released because of the successful results for the routine release functionality testing across the totality of those in-scope lots, as well as the supplemental testing performed on lot 5GR446 showing no additional similar defects occurred upon activation. The completed sample testing for all in-scope lots is set forth below to illustrate the large number of samples tested as part of routine lot release, as well as the marginal value of supplemental destructive testing across the other (b) (4) in-scope lots due to the already large original sample size.

| Batch ID | Original Samples Tested | Original UQL | Supplemental Sampling | New UQL | Assurance Gain from Supplemental Sampling |
|---|---|---|---|---|---|
| 5GR446 | (b) (4) | (b) per (b) (4) UQL (b) (4)% | (b) (4) | (b) per (b) (4) UQL (b) (4)% | (b) (4)% |
| (b) (4) in-scope Lots | (b) (4) | (b) per (b) (4) UQL=(b) (4)% | (b) (4) per Lot (if performed) | (b) per (b) (4) UQL=(b) (4)% | (b) (4)% |

The (b) (4) other lots within the scope of this investigation ( (b) (4) ) have all expired. None of these lots had any confirmed complaints.

As communicated in the Final FAR on 20NOV2015, a Design of Experiment (DOE) was conducted at (b) (4) to investigate (b) (4) and their impact on (b) (4) of the (b) (4) used to manufacture the (b) (4). The results of (b) (4) and (b) (4) impacted the (b) (4) which is undesirable. (b) (4) before (b) (4). The DOE result showed there was no processing configuration that would (b) (4) without affecting the (b) (4) properties of the (b) (4).

Although the routine testing done under our release procedures is robust, we recognize that when a product component has caused an OOS, additional physical testing of all other lots in which it has been used is appropriate. Accordingly, to address this Observation, SOP-QLA-MQA-00720, *Event and Deviation Reporting (ER & QAR)*, will be updated by 31MAY2017 to assure consistent application across lots in the scope of an investigation when additional testing is performed to evaluate potential quality impact. As an additional routine process control, the standard sampling plan for EpiPen finished good functionality testing is (b) (4) to (b) (4) units per assembled lot by 30APR2017. This will (b) (4) the AQL from (b) (4) to (b) (4)

**OBSERVATION 1C**

*Your investigation PR 24844 did not fully address the issue of the large number of low fills for atropine in Lot 6M1454 of Atropine and Pralidoxime Chloride Injection (ATNAA). For this lot, your firm identified (b) (4) units with low fill in the front chamber (Atropine). The (b) (4) other batches inspected during the (b) (4), had a low fill range of (b) (4) units per batch. No new CAPAs were identified for the Lot 6M1454 investigation and your investigation concluded the filler was operating within its capabilities.*

**Response to Observation 1C**

Investigation report PR 24844 was issued following the discovery that lot 6M1454 exceeded the defect alert limits for the percentage of defects rejected during the 100% manual visual inspection (MVI) process. Exceeding the defect alert limit is not necessarily indicative of a failure of the inspection or manufacturing process. The inspection process and the use of defect alert limits provide the opportunity to respond to special cause variation and continuously

improve the process. PR 24844 documents the 100% MVI process that was followed for lot 6M1454 and relates the results that were obtained. The MVI process for this lot conformed to the process in the approved ATNAA NDA 021175 (reference PAS S-032, approval 16NOV2016) and DuoDote NDA 021983 (reference PAS S-022, approval 03NOV2016). As discussed in the investigation, this lot did not meet the defect alert limits for critical defects due to the number of units categorized as low fill atropine defects; there were a total of (b) (4) such defects rejected during the MVI and filling processes.

Investigation PR 24844 followed the required template to ensure that a thorough investigation was completed. The issue was escalated as required by the procedure and a determination was made that an investigation was required; during the investigation, the lot was placed on hold. As part of the escalation process, the potential for impact to marketed product was evaluated, and it was determined that there was no impact to marketed product.

The investigation focused on the critical defects identified during MVI. As noted in the investigation, the approved manufacturing process includes a number of in-process controls to prevent low fills. The investigation determined that there were three potential root causes for low fill atropine:

- (b) (4)
- (b) (4)
- (b) (4)

The investigation did include a two year historical review of prior incidents where batches exceeded the alert limits for critical defects, reviewed the CAPAs implemented to address those issues, and discussed whether those CAPAs would apply to help reduce the incidence of the low fill atropine defect. The report specifically identified one on-going CAPA – the purchase, qualification, and installation of a (b) (4) – that was still in progress and would help minimize the number of incidences of low fill atropine.

However, the investigation did not document a number of on-going continuous improvement initiatives that were in process that will help further minimize the incidence of low fills. These projects included modifications to the (b) (4) that have since been qualified and were submitted to FDA in a CBE-30 on March 14, 2017; the changes are targeted for implementation by the end of April 2017 and include the following:

- Modification of the program to require acknowledgement by (b) (4) and other critical faults.
- Addition of a (b) (4) fault so that misalignment of the (b) (4), causing the (b) (4) and activate a fault message to (b) (4) the (b) (4) that could result in low fills.
- (b) (4) following any of (b) (4) separate machine fault codes that (b) (4) and possible (b) (4)
- (b) (4) and (b) (4) so that the (b) (4) does not (b) (4) and (b) (4)

- (b) (4) of units (b) (4) occurs during (b) (4) since the (b) (4) can (b) (4) and (b) (4)

The statement in the investigation that the filler was operating within its capabilities was meant to describe the performance of the filler at that time. The single preventive action in the investigation plus the ongoing initiatives have all been designed to further reduce low atropine fills.

PR 24844 was re-opened and revised to include the full complement of continuous improvement projects. The investigation procedure (SOP-QLA-MQA-00720) will be revised by 31MAY2017 to require that all ongoing preventive actions that address root cause are included in an investigation report.

In addition, PR 24844 did not include a discussion regarding the historical process trend for this defect and whether lot 6M1454 was within the process trend. To ensure this information is included in investigations, SOP-QLA-MQA-00720 will also be revised by 31MAY2017 to require that deviation investigators implement the use of trending tools such as control charts to identify when the item or event being investigated differs from the historical process trend as an aid in the investigation process.

The Response to Observation 2A provides further discussion on the MVI results for lot 6M1454, including limitations in the use of MVI as a surrogate for (b) (4) and finished product test results for quantitative measures of atropine fill.

**OBSERVATION 2**

*Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically,*

**OBSERVATION 2A**

*Your procedures and practices allow your employees to repeatedly inspect lots of ATNAA to cull out defective units. These repeated 100% visual inspections however, do not remove all of the defective units.*

**Response to Observation 2A**

ATNAA/DuoDote Manual Visual Inspection Process

The process flow and acceptance criteria for the manual visual inspection (MVI) of ATNAA/DuoDote are described in the approved ATNAA NDA 021175 (PAS S-024, approved 15MAR2014) and DuoDote NDA 021983 (PAS S-015, approved 19DEC2014). (Note: DuoDote is an identical product to ATNAA, with the exception of being labeled as "DuoDote".) The MVI process as described in the supplements was revised and changed following extensive work in 2013-2014 and discussions between FDA, MMT, and the Department of Defense. MVI for all

ATNAA/DuoDote lots released subsequent to the approval of these supplements have conformed to this approved process. It is important to note that per the approved process and as described below, each lot of ATNAA/DuoDote can (b) (4). If the results from the (b) (4) do not meet the acceptance criteria specified in the NDAs, that lot is rejected.

The industry literature recognizes that 100% of defects may not be removed during 100% MVI. USP <1790>, Visual Inspection of Injections (official 01AUG2017), states; "Inspection is a probabilistic process and detection rates <100% are to be expected, especially for smaller or low-contrast defects." While this USP chapter addresses inspection for visible particles, the concepts also apply to visual inspection of other attributes.

Following is a summary of the approved process for the 100% MVI of ATNAA/DuoDote:

- 100% of the basic units are inspected by qualified inspectors. Critical, major, and minor defects are culled and rejected from the batch.
- A Normal Acceptance Quality Limit (N-AQL) sample of (b) (4) units is taken from the accepted units and inspected by Quality Control (QC).
- The percentage of units rejected as critical, major, and minor defects during 100% MVI is also assessed vs. defect alert limits that are based on 2008 PDA Industry Survey.
- The results of the initial 100% MVI are reviewed and the following actions are taken:
    - If N-AQL sample passes and defect alert limits are not exceeded – the lot proceeds to assembly.
    - If N-AQL sample passes and the defect alert limits are exceeded - a (b) (4) sample of an (b) (4) units is taken from the accepted units and examined by QC.
        - If (b) (4) sample passes – the lot proceeds to assembly.
        - If (b) (4) sample does not pass for critical defects – the lot proceeds to a (b) (4).
        - If (b) (4) sample does not pass for major or minor defects – the lot proceeds to a (b) (4) based on outcome of an investigation.
    - If N-AQL sample does not pass and defect alert limits are exceeded – the lot proceeds to a (b) (4).
    - If N-AQL sample does not pass and the defect alert limits are not exceeded – the lot proceeds to a (b) (4).
- If a (b) (4) was required, after the (b) (4), a (b) (4) (b) (4) units is taken from the accepted units and examined by QC.
    - If (b) (4) sample passes – the lot proceeds to assembly.
    - If (b) (4) sample does not pass for critical defects – the lot is rejected.
    - If (b) (4) sample does not pass for major or minor defects – the lot is rejected or proceeds to assembly based on outcome of an investigation.
- For any of the steps above, when either an N-AQL or (b) (4) sample does not pass or when defect alert limits are exceeded for an initial 100% MVI or (b) (4) an investigation is required.

- If missing drug is found at any step in the process after the completion of 100% MVI, the lot is rejected.

Greater detail about the defect alert limits and AQL sampling is below.

Defect Alert Limits

After 100% MVI, all defects are classified, totaled, and compared against established alert limits for critical, major, and minor defects. Process alert limits would commonly be based on process capability, e.g. (b) (4). MMT uses a (b) (4)% for critical defects for MVI. This limit was based on a conservative interpretation of industry standards published in a PDA 2008 Industry Survey. This (b) (4) is more conservative and triggers a response for more batches than process capability limits would for the current ATNAA/DuoDote process.

Exceeding the defect alert limit is not necessarily indicative of a failure of the inspection or manufacturing process, particularly in light of the use of the (b) (4) rather than one based on process capability. The inspection process and the use of conservative defect alert limits provide the opportunity to respond to special cause variation and continuously improve the process.

AQL Samples

Following the initial 100% MVI, an N-AQL statistical sample is taken from the accepted units and examined by QC. MMT utilizes a critical N-AQL of (b) (4)% for MVI and a sample size of (b) (4) units. As a result, if a critical defect is found in the N-AQL, the lot cannot be accepted for further processing, without the performance of a (b) (4).

If a lot does not meet the defect alert limits after the initial 100% MVI or if (b) (4) is performed for any reason, a lot must pass the criteria for a (b) (4) sample of (b) (4) units with (b) (4) critical defects allowed. This (b) (4) sample size is equivalent to an AQL of (b) (4)% for critical defects.

ATNAA/DuoDote MVI Process Controls

The MVI process for ATNAA/DuoDote is aligned with cGMP industry practices. Multiple controls are in place to ensure high performance of the MVI process, including the following:

- There is a robust program for the qualification of our manual visual inspectors. Requirements of the Inspector Qualification Program include:
  - A (b) (4) thereafter.
  - Training on all MVI procedures and defect manuals, including a knowledge assessment by a qualified trainer.
  - A practice inspection utilizing a (b) (4).
  - Successful inspection of (b) (4) to demonstrate inspection proficiency.

  - The qualification test kits contain units (b) (4) .
  - Each inspector is required to complete a requalification (b) (4) by successfully inspecting (b) (4) .

- The site employs a number of environmental controls to assist the inspectors in the inspection process. These processes were enhanced in 2013 and include:
  - (b) (4) , including lighting, are designed to facilitate optimal inspector focus.
  - (b) (4) inspectors and reduce potential distractions.
  - Adjustable seating to allow proper posture and alignment while inspecting.
  - Senior inspectors manage and control the inspection work center environment.

- The site also employs a number of procedural controls around the MVI, including the following:
  - *Multichamber Auto-Injector Basic Unit Defect Manual*, RM-MAN-INS-10000, which provides Inspection personnel with the classifications, definitions, and descriptions of basic unit defects, including pictures to ensure consistent understanding of each defect.
  - SOP-MAN-INS-00031, a pictorial diagram of the inspection process, is posted (b) (4) as a reference for the inspectors.
  - (b) (4) , ensure a minimum inspection time of (b) (4) seconds for each unit, assuring that inspectors take the time to perform the necessary inspection steps.

MVI Process Performance, January 2015 – February 2017

A summary of data related to the MVI process for basic units of ATNAA/DuoDote inspected between 01JAN2015 and 21FEB2017 can be found in the table below.

| MVI Process Step | AQL Sample or 100% MVI Rejects | Defect Category | # of Lots That Met Limits / All Lots Inspected | % of Lots That Met Limits |
|---|---|---|---|---|
| Initial 100% MVI | 100% MVI Rejects | Critical | (b) (4) | |
| | | Major | | |
| | | Minor | | |
| | N-AQL Sample | Critical | | |
| | | Major | | |
| | | Minor | | |
| | (b) (4) Sample | Critical | | |
| | | Major | | |
| | | Minor | | |
| (b) (4) (b) (4) MVI | (b) (4) Sample | Critical | | |
| | | Major | | |
| | | Minor | | |

* Note: As a clarification, the number of re-inspected batches in this period was (b) (4) and not (b) (4) as noted in the Observation.

The data table shows that the initial 100% MVI inspection process is robust in culling defects as evidenced by the results for N-AQL samples: (b) (4)% and (b) (4)% of lots met N-AQL acceptance criteria for critical and major/minor defects, respectively.

As previously discussed, due to the conservative nature of the defect alert limits, (b) (4)% of lots ((b) (4) of (b) (4)) required an (b) (4) sample of (b) (4) units after the initial 100% MVI. The majority of these (b) (4) lots required the (b) (4) sample due to not meeting the in-process defect alert limits for minor defects. Minor defects are defined as defects that could through use, cause discomfort to user/patient but where the product functions as intended.

The data for the (b) (4) samples for these (b) (4) lots also show that the initial 100% MVI inspection is robust in culling defects (b) (4)%, (b) (4)%, and (b) (4)% of lots meet (b) (4) acceptance criteria for critical, major, and minor defects, respectively. This is further demonstrated by data from the (b) (4) samples that followed a (b) (4) MVI that was performed for (b) (4) lots: (b) (4)% and (b) (4) lots met (b) (4) acceptance criteria for critical and major/minor defects, respectively. Only (b)% of lots (b) (4) ) did not meet the acceptance criteria for the approved MVI process, including inspection, AQLs, and (as necessary) (b) (4) and/or (b) (4) These (b) (4) lots were rejected accordingly as per SOP-QLC-SQC-00328, *ATNAA/DuoDote QA Visual Audit and Final Product Inspection with AQL Sampling*.

Observation 2A1 and 2A2 reference ATNAA lots 6M1133 and 6M1454, respectively. These two lots provide examples of how the MVI controls ensure that the process is monitored and

effective at ensuring batch quality expectations. Both of these lots passed the N-AQL but exceeded established defect alert limits during the initial 100% MVI. Due to the failure of these lots to meet defect alert limits, (b) (4) samples of (b) (4) units were pulled and did not meet the acceptance criteria due to one critical defect found for each lot, respectively. Both lots were (b) (4) and (b) (4) samples pulled. The disposition of these lots was as follows:

- Lot 6M1133 did not meet acceptance criteria for (b) (4), as critical defects were found during the (b) (4). As per SOP-QLC-SQC-00328, lot 6M1133 was rejected.
- Lot 6M1454 met acceptance criteria for the (b) (4). As per SOP-QLC-SQC-00328, lot 6M1454 was released for further processing.

Drivers of MVI Performance

The ATNAA/DuoDote basic unit contains atropine solution in the front chamber and pralidoxime chloride in the rear chamber. A (b) (4) is (b) (4) For those lots that did not meet the critical defect alert limit (b) (4) lots per the table above) or did not meet the AQL acceptance criteria (e.g., (b) (4) lots for the N-AQL sample per the table above) for critical defects, the primary driver is the low fill atropine defect.

MVI is not a quantitative measurement process. Per RM-MAN-INS-10000, the inspectors utilize a (b) (4) as a reference point to identify a low fill atropine defect. If the meniscus of the atropine volume is (b) (4), the unit is considered a low fill atropine defect. To demonstrate the use of this (b) (4) (b) (4) reference point, a study (RP-721 approved 17NOV2014; included in NDA 021175/ S-027 and NDA 021983/ S-018) was executed wherein (b) (4) units were filled with (b) (4) of atropine formulation (the (b) (4) in the atropine filling batch record) and visually inspected. The meniscus of the atropine solution was (b) (4) units, validating the use of the (b) (4) as a conservative reference point for low fill atropine. However, these results also demonstrate that the use of this (b) (4) does include the potential for some false rejects.

The following quantitative measures verify that the (b) (4) Filler Machine process for filling atropine is in a good state of control:

- Of (b) (4) units (b) (4) during filling of all ATNAA/DuoDote lots produced since January 2015, only (b) units (b) (4)%) were less than the (b) (4) action limit of (b) (4) g. The Cpk and Ppk for atropine fill (b) (4) are (b) (4) and (b) (4), respectively, indicating good process capability.
- Atropine (base) delivered dose testing has been conducted on all assembled ATNAA/DuoDote lots produced since 30JUN2016, when this testing was initiated. For (b) (4) samples (b) (4) replicates per lot) tested to date, individual replicates ranged from (b) (4) – (b) (4) mg, well within the approved specification of (b) (4) – (b) (4) mg (b) (4)(b) (4)% of label claim).

MVI Process Improvements

To assess the drivers of MVI performance and further improve the robustness of the MVI process for ATNAA/DuoDote, MMT will take the following actions:

- An attribute analysis capability study for the ATNAA/DuoDote MVI process will be performed. Any improvement opportunities will be incorporated into a process continuous improvement plan by 31AUG2017.
- (b) (4) to further improve (b) (4) and enhance the inspection environment by providing (b) (4) for inspectors. These (b) (4) will be implemented by 30JUN2017.
- (b) (4) inspector audits will be implemented for each qualified inspector to (b) (4) performance on a defined frequency.
- AQL sampling will be adjusted by 31JUL2017 so that results of the sampling are (b) (4). This will enable direct and immediate performance feedback (b) (4).
- As discussed further in Response to Observation 4C, Machine Capability studies will be performed on the (b) (4) equipment.

**OBSERVATION 2A1**

*Based upon review of production data, (b) (4) % of the batches from the ATNAA / DuoDote process (b) (4) out of (b) (4) batches inspected between 1 JAN 2015 and 21 FEB 2017) are not complying with the specified criteria for percent defect for critical, major, or minor defects during the 100% manual inspection. Your firm performed an additional 100% inspection for (b) (4) batches out of (b) (4), approximately (b) (4) % of the time. Additionally, there has been at least one batch, Lot 6M1133, which was subsequently rejected because it did not meet the criteria for a (b) (4) after the performance of a (b) (4) 100% inspection.*

**Response to Observation 2A1**

MVI for lot 6M1133 was completed per the approved NDA process; the process is described above in the Response to Observation 2A. The details of the MVI and AQL sampling for this lot are summarized below.

- Lot 6M1133 exceeded the defect alert limits after the initial 100% MVI and, a (b) (4) sample was taken accordingly. The (b) (4) sample of (b) (4) units (taken after the initial 100% MVI) did not meet acceptance criteria due to one critical defect, leaking unit due to breach in stopper. Per the approved process, the lot was (b) (4).
- During the single repeat of 100% MVI, two low fill atropine units were rejected.
- Per the procedure, a (b) (4) sample of (b) (4) units was taken after the (b) (4) 100% MVI. The (b) (4) did not meet acceptance criteria due to two low fill atropine defects.
- Per SOP-QLC-SQC-00328, and the approved MVI process, lot 6M1133 was rejected.

**OBSERVATION 2A2**

*ANTAA [sic] Lot 6M1454, exceeded the alert limits for critical and minor defects during the initial 100% visual inspection. It passed the initial Acceptable Quality Limit (Visual (b) (4) QA performs on (b) (4) of the "acceptable" units. Since this lot exceeded your defect alert limits, your firm performed a (b) (4) ) on (b) (4) of the "acceptable" units. During the (b) (4), the QA Inspector found one (1) unit with a low fill in the front chamber which is a critical defect. Therefore, your firm performed another 100% visual inspection and found 20 units with critical defects, 30 with major defects, and 907 with minor defects. (b) (4) was performed on the "acceptable" units and three minor defects were found. This batch was released on 19 JAN 2017 by your Quality Assurance Unit.*

**Response to Observation 2A2**

MVI for lot 6M1454 was completed per the approved NDA process; the process is described above in the Response to Observation 2A. The details of the MVI and AQL sampling for this lot are summarized below.

- Lot 6M1454 exceeded the defect alert limits after the initial 100% MVI and a (b) (4) sample was taken accordingly. The (b) (4) of (b) (4) units (taken after the initial 100% MVI) did not meet acceptance criteria due to one critical defect, low fill atropine.
- During the single repeat of 100% MVI, 20 critical defects were rejected, 11 low fill atropine defects and 9 critical unclassified defects (the senior inspector performing the classification could not confirm the defect in the rejected unit). The inspectors also rejected an additional 937 units (30 major defects and 907 minor defects).
- Per procedure, the (b) (4) sample of (b) (4) units (taken after the (b) (4) 100% MVI) met acceptance criteria.
- Per SOP-QLC-SQC-00328, and the approved MVI process, lot 6M1454 was approved for further processing.

**OBSERVATION 2B**

*Your manual visual inspection programs are deficient since:*

**OBSERVATION 2B1**

*There is no evaluation of the efficiency / effectiveness of an individual performing repetitive inspection over time for your basic units.*

**OBSERVATION 2B2**

*The (b) (4) certification process for detection of defects in your basic units is not currently performed at the (b) (4) in order to evaluate the impact of fatigue, if any, upon defect detection capability.*

**Response to Observation 2B1 and 2B2**

The majority (b) (4)% for EpiPen and (b) (4)% for ATNAA) of inspectors that completed their initial MVI Qualification from 2015 to present performed (b) (4) required qualification tests (b) (4). A qualification test kit contains (b) (4) units that would be individually inspected during a single qualification test. Performing back to back qualification tests in one day would result in inspecting (b) (4) units, which exceeds the production standard of (b) (4) units per inspector (b) (4). This would have subjected these inspectors to fatigue conditions during their initial qualification process and represents a worst-case scenario when compared to routine work scheduling.

Per the MVI batch records, a (b) (4) break is required for (b) (4) of inspection, to reduce eye strain and inspector fatigue. In addition, inspectors are provided (b) (4) breaks and (b) (4).

The inspection qualification procedure, SOP MAN-INS-00029, *100% Manual Inspection Qualification,* will be revised by 31MAY2017 to add a specific requirement for the simulation of fatigue conditions during inspector qualification/re-qualification for all product lines.

**OBSERVATION 2B3**

*The process for incoming (b) (4)" introduced into EpiPen manufacturing does not specify the maximum amount of time (b) (4) that an inspector is allowed to perform visual inspection. Current established practice does not limit inspection time to prevent errors caused by fatigue and loss of concentration. The operators do not have required break times and are not qualified for this inspection.*

**Response to Observation 2B3**

All glass lots received at MMT are subject to incoming quality control testing per Quality Control Test Report 4013004. This incoming acceptance testing includes visual inspection for defects and dimensional specifications. Colleagues that perform incoming acceptance testing for (b) (4) reference RM-QLC-SQC-10555, *Defect Reference Manual for the (b) (4) Component*. The reference manual includes photos, defect classifications, definitions, and descriptions of (b) (4) defects. Per a review of training records, all colleagues who perform this activity have completed training for RM-QLC-SQC-10555.

Evaluation of the (b) (4) during the (b) (4) operation in the Clean and Prep area is governed by SOP-PRO-CLP-00005, (b) (4) *at* (b) (4). This procedure describes the process for (b) (4) evaluation during a (b) (4) step that is conducted prior to (b) (4) washing and subsequent filling operations. This evaluation is not an inspection of individual units to assure end product quality, but rather a (b) (4) that is performed to improve the downstream manufacturing step process flow and yields. As such, all of the controls that apply to the inspection of individual product units (e.g., visual acuity testing, evaluation time duration, etc.) do not apply to the (b) (4). Any defects found during the (b) (4) are rejected from the lot. Per a review of training records, all colleagues who perform this activity have completed training for SOP-PRO-CLP-00005.

After units are filled, all finished basic units undergo (b) (4) % inspections which include the rejection of individual units with potential (b) (4) defects. The (b) (4) % inspections are:

(b) (4)

- 100% MVI performed by qualified inspectors- includes inspection for multiple (b) (4) defect types

Inspectors that perform (b) (4) and MVI of finished basic units are qualified per SOP-MAN-INS-00029, *100% Manual Inspection Qualification*. Qualification requires (b) (4) testing. Qualification also requires the (b) (4) containing acceptable units and defects, with (b) (4) and (b) (4) thereafter. Per a review of training records, all inspectors who perform (b) (4) or MVI of finished units have completed training requirements per SOP-MAN-INS-00029.

To further improve the process robustness for the (b) (4) during the execution of SOP-PRO-CLP-00005, the following improvements will be made to procedures and the training process:

- A job aid which includes (b) (4) and further details for the steps performed during the (b) (4) will be created by 07JUN2017.
- A new On-The-Job (OJT) training document will be developed and implemented by 07JUN2017 for all colleagues that perform (b) (4). The new OJT will require review of the job aid, review of SOP-PRO-CLP-00005, and hands on training.

**OBSERVATION 3**

*Procedures describing the handling of all written and oral complaints regarding a drug product are not established, written and followed. Specifically,*

**OBSERVATION 3A**

*Your firm has not documented rationale why (b) (4) complaints of a similar nature on the same lot are necessary to identify a trend per your procedure Product Complaint Handling SOP-QLC-QLE-00702.*

**Response to Observation 3A**

SOP-QLC-QLE-00702, *Product Complaint Handling*, currently states that (b) (4) complaints of a similar nature on the same lot shall be considered a trend.

A statistical analysis will be completed by 15MAY2017 with at least 2 years of complaint data for all products and all complaint sub-classes. Based on the analysis, statistically based lot trend alert limits will be identified for complaint sub-classes. SOP-QLC-QLE-00702 will be revised by 31MAY2017 to clarify that site personnel can and should take action to address any combination of complaints, no matter the number, that appears to signal a trend or issue and to establish the following expectations with respect to alert limits:

- statistically based alert limits for the number of complaints of a similar nature for the same lot for all products and all complaint sub-classes
- a requirement that lot trend alert limits are based on statistical analysis of historical complaint data
- a requirement that the statistically based lot trend alert limits be reviewed at least annually

Please refer to Response 3C for additional information regarding complaint trending and risk assessment.

**OBSERVATION 3B**

*Complaint classifications, listed in GPB-QS1073 Prioritization of Pfizer Product Quality Complaints, are assigned prioritization classifications that are not commensurate with the associated clinical risk (e.g. no dose delivered) based on the alleged complaint. Three complaint prioritization classifications (Expedite, High, Normal) are assigned to complaint classifications. These prioritization classifications dictate the speed and thoroughness of the investigations conducted by your firm. There are at least ten product complaint classifications that do not adequately reflect the associated risk including, but not limited to, 'Spontaneous Activation' classified as Normal, 'Container Broken/Cracked/Leaking Prior to Use' classified as Normal, and* [redacted] *to Injection' classified as Normal.*

**Response to Observation 3B**

All quality complaints received by Pfizer are reviewed by a product quality complaint triage group. The triage group assigns a classification code which describes the nature of the quality complaint and a priority code (expedited, high, and normal) which determines the initial complaint processing timelines and requirements for notification to management, if applicable. Expedited complaints require more rapid initial processing due to the potential need for certain specific regulatory notifications, including NDA FARs and Biological Product Deviation Reports in the U.S.

All quality complaints that meet the requirement for a site investigation, regardless of the assigned priority, are thoroughly investigated in order to determine root cause, identify corrective actions, and prevent recurrence. For expedited prioritized complaints, a preliminary investigation is performed within [redacted] of the complaint at the investigating site. The intent of the timeframe and preliminary investigation is to allow the site to determine the need for submitting the specific regulatory notifications described above within required timeframes.

A prioritization of expedited is assigned to potentially serious product complaint allegations for the purpose of accelerating the initial complaint investigation and facilitating submission of a NDA FAR, if necessary. The NDA FAR regulation criteria and the complaint classifications that may fall within those specific criteria will require an expedited status for the purpose of filing the NDA FAR within (b) (4) for:

- any incident that causes the (b) (4),
- (b) (4),
- a significant (b) (4),
- (b) (4) in the distributed drug product, and
- (b) (4) distributed batches of the drug product to (b) (4).

As an action, Pfizer procedure GPB-QS1073 will be updated by 30JUN2017 to clarify the purpose of the expedited complaint process. As part of the update, all complaint classifications associated with devices and combination products will be evaluated to ensure alignment to the requirements of the specific regulatory notifications described above. In addition, all complaint classifications associated with the products manufactured at MMT will also be evaluated to ensure that any product specific exceptions regarding prioritization are included in the update to GPB-QS1073. MMT site procedure, SOP-QLC-QLE-00702, *Product Complaint Handling*, will also be updated by 15JUL2017 to reflect the clarifications in GPB-QS1073 regarding the purpose for expediting complaints.

**OBSERVATION 3C**

*No safety or risk assessment has been completed to establish the acceptability of the mean complaint rates received by Pfizer Corporate, which is utilized by your firm to establish the upper and lower confidence limits of complaint.*

**Response to Observation 3C**

As discussed during the inspection, the intended goal of the Pfizer Corporate complaint (b) (4)) trending approach is to detect (b) (4) changes to product quality complaint counts using statistical methodology. All closed and in-progress product quality complaints received into the global complaints database (b) (4) are evaluated for deviation from the expected (b) (4) complaint counts and thresholds to identify emerging trends per (b) (4) procedure. When any of the statistically determined thresholds are exceeded, a Complaint Trend Alert is generated, further evaluated to identify Complaint Trends, and then as appropriate, escalated to management and the site or center Quality authority responsible for the product. Trend Notifications are investigated by the responsible Quality authority to determine the cause, impact, potential CAPAs, and whether a regulatory notification is required.

MMT is engaging experienced independent consultants with significant experience with medical device quality systems to conduct an assessment of the MMT quality systems, including Complaint Management. This assessment is targeted for completion by 31AUG2017, with

creation of an action plan with timeframes for corrective actions targeted for completion by 30SEP2017.

As discussed in the Response to Observation 6A3, a Risk Assessment will be performed including Safety/Medical/Clinical, to document the rationale for the ranges of the essential performance inputs and their criticality/severity based on the emergency, life-saving intended use of the product. This risk assessment will also establish acceptable mean complaint rates and will be reviewed at a minimum of annually as part of the Annual Product Records Review process. The risk assessment is targeted to be completed in 31JUL2017.

**OBSERVATION 4**

*Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established. Specifically, insufficient statistical assessments were in place for establishing, controlling, and verifying process capability and product characteristics.*

**OBSERVATION 4A**

*Your firm provided no rationale for the acceptability of your sampling plan at lot release based on the risk associated with releasing defective product. The AQL (Acceptable Quality Limits) sampling plan and associated* (b) (4) *%) is not commensurate with the product risk based on intended use and design inputs of the product.*

**Response to Observation 4A**

The AQLs, and associated (b) (4), for critical tests for the current NGA product and applied to the (b) (4) product were filed and approved by the agency in the EpiPen NDA; NDA 19-430, approved on 22DEC1987 and subsequent supplements, PAS S-043, approved on 14NOV2007 and CBE S-049 approved on 20NOV2009. The supplements to the NDA for the NGA platform were approved by the agency with these AQLs and have been followed by MMT in the required product specifications. These same AQLs were used and were applied to the (b) (4) product specifications. For current production: Note that these sampling plans (b) (4), i.e. the sampling plan requires (b) (4) critical defects or the batch will be rejected, regardless of AQL. The AQL is used solely to define sample size for testing as (b) (4) critical defects will be allowed. The current AQL of (b) (4) sampling plan (for critical defects) will be modified (b) (4) AQL of (b) (4) for assembled final product functionality testing. This new sampling plan will be implemented by 30APR2017.

Furthermore, a risk assessment will be completed by 31JUL2017, including representatives from the Safety/Medical/Clinical groups to document essential attributes for intended use and their criticality. For those essential characteristics that are confirmed in the risk assessment and defined as critical in Table 2 of Response 6A, there will be a plan implemented to conduct testing based on system level reliability.

**OBSERVATION 4B**

*Your firm does not currently distinguish the failure modes of rejected components/units that are collected in reject bins on the EpiPen manufacturing assembly line. In addition, your firm does not currently track or trend the rejects from the EpiPen assembly manufacturing line and there are no action limits associated with the number or type of rejects.*

**Response to Observation 4B**

The assembly of the EpiPen auto injector is performed on Next Generation Auto-Injector (b) (4). Basic units (b) (4) for the EpiPen auto injector assembly process are performed (b) (4) of every batch as listed in the table below. These challenges ensure the performance of the (b) (4) systems. In addition, (b) (4) testing during (b) (4) to monitor the quality of each batch.

| (b) (4) | (b) (4) Description | Configuration |
|---|---|---|
| | (b) (4) Test | (b) (4) |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) -Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) ) | |
| | (b) (4) Test | |
| | (b) (4) Test | |
| | (b) (4) Test | |

Currently, as per the design of the (b) (4) Assembly machine, there are (b) (4) into a common eject bin. Currently, the number of ejected units from (b) (4) is not counted separately. The total number from each of the common eject bins is recorded in the batch record for accountability purposes.

As discussed in Response 4C2 and 4C3 below, a procedure will be developed by Operational Excellence, Manufacturing, and Quality to require routine (b) (4) trending for ATNAA and EpiPen and to assess performance variability by 30JUN2017. This routine trending will include ejects from the (b) (4) MMT will trend eject levels from (b) (4) for multiple lots and will develop action limits based upon process capability. The action limits will be included in all batch records for the EpiPen Assembly processes by 30SEP2017. Trend reporting, including ejects from the (b) (4) Assembly machine, will be

incorporated into periodic reviews at Site Quality Review Team (SQRT) meetings by 31OCT2017 and included in the 2018 Annual Product Records Review (APRR) for continuous improvement.

Currently, the site is manufacturing (b) (4) products (EpiPen, EpiPen Jr., and (b) (4) ) and ATNAA/DuoDote. The above-referenced procedure will at present apply to those products. The site has in the past manufactured a number of other products. If and when production resumes for any one of these other products, MMT will evaluate the routine (b) (4) trending that should be added to the manufacturing process for that product, with a documented assessment.

**OBSERVATION 4C**

*Your firm failed to routinely evaluate ongoing state of control of the equipment and process. For example,*

**OBSERVATION 4C1**

*The capability and suitability of equipment to produce conforming units was not assessed. Specifically, process capability evaluations did not reflect inherent capability of the process equipment to produce conforming units. Instead, you only calculated process capability after a large number of defects were inspected out of the batch.*

**OBSERVATION 4C2**

*Your firm failed to adequately analyze data to determine process points in which excessive variation occurred and defective units were produced.*

**OBSERVATION 4C3**

*Your firm lacked sufficient ongoing trending of numerous in-process attributes that are critical to the quality of the finished product. For example, there was insufficient ongoing trending to periodically assess (e.g. process trending reports, Annual Review) process performance to promptly detect atypical variability that may affect product quality.*

**Response to Observations 4C1, 4C2 and 4C3**

MMT acknowledges the importance of evaluating our ongoing state of control, and we are engaged in multiple efforts to improve our procedures. To this end, MMT has continued in particular to implement continuous improvements to the production processes for products that rely on MVI for the detection of defects.

Per a prior commitment, ATNAA was the first product to undergo a thorough end-to-end equipment and process review. Black Belt projects were initiated in 2013 that focused on the (b) (4) process of the filling machine and MVI process. Identification of root causes for ATNAA no fills/low fills from filling were identified and corrections implemented. Process Maps and Design of Experiment were conducted to identify the changes required. Key examples

are the decision to [redacted], the equipment filling machine critical fault code identification, and appropriate software changes. Similarly, enhancements to the inspection process included [redacted]. Other enhancements for the MVI process included [redacted]; development of a training standard for inspection techniques and qualification for inspectors, and standardization of defect collection and classification methodology. These PAS changes were submitted and approved. Subsequent to the PAS approval, CAPAs were implemented to complete other initiatives to replace filler PLC and associated HMIs to meet contemporary standards. MMT continued its focus on component preparation for the filling operation to reduce filling machine variability for low fill/no fill units. A [redacted]. In response to this Observation, MMT will continue to evaluate with the OEM further enhancements to reduce filling machine variability that can cause product defects for all fill equipment.

In addition, a new procedure to conduct routine Machine Capability studies has been drafted and will be approved by 15MAY2017. Updates to the Process Maps are also being developed for the products currently being manufactured at the site, ATNAA and EpiPen, to identify process input variables that can be further evaluated to enhance process capability. The initial Machine Capability study to be conducted under the scope of the new procedure will be for the [redacted]. A detailed roll-out plan for all equipment to be studied will be approved by Manufacturing and Quality by 30MAY2017. As an outcome of the capability studies, Six-Sigma projects will be employed to reduce variability where improvement areas are identified. Results from the capability studies will be incorporated into periodic reviews of Site Quality Review Team (SQRT) and Annual Product Record Review (APRR).

Trending of defects from MVI is currently ongoing for the basic units for ATNAA and EpiPen as a reactive measure. This trending has led to Six Sigma improvements for two defects observed in the basic unit for ATNAA. [redacted] Defects were observed on the ATNAA body that was caused by the [redacted] process, where [redacted]. The second defect was an increase in the [redacted] of ATNAA after filling. The [redacted] process was performed to reduce these defects in both cases. Defect data will continue to be reviewed ongoing to trend the defects that are critical to the product. In response to the Observation, a new procedure will be developed by MMT to require routine [redacted] trending of critical parameters to assess performance variability for ATNAA and EpiPen by 30JUN2017. [redacted] trending at the site will be in place by 30AUG2017 for identified critical processing areas. A review of these trend reports will be incorporated into periodic reviews at SQRT meetings as well as in the APRR.

**OBSERVATION 5**

*Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures. Specifically, your analysis of the quality data used to identify existing and recurring quality problems does not include an analysis of complaints based on finished product lots, manufacturing dates or component lots to identify existing or recurring quality problems. Your analysis is presented and discussed* (b) (4) *during management review meetings, is currently conducted by totaling complaints by* (b) (4)

**Response to Observation 5**

As discussed in the observation, the current site complaint trend reports include counts of complaints by (b) (4). These trend reports are reviewed at Site Quality Review Team (SQRT) meetings and are also included in the Annual Product Records Reviews (APRRs) for identification of corrective actions. SOP-QLC-QLE-00702, *Product Complaint Handling*, requires the following information in each complaint investigation report to identify recurring issues or trends:

- The number of complaints of a similar nature on the same lot is verified to determine if there is a trend for the lot.
- The number of complaints of a similar nature for the product line is verified to assess whether there is a trend for the product.
- The number of complaints of a similar nature for all product lots that used the same relevant component(s) lot(s) as the complaint lot is verified. Each of the associated complaint investigations are reviewed to assess whether the complaint is recurring.

Complaint trend reports based on finished product lots, manufacturing dates, and component lots will be implemented by MMT. These additional site trend reports will be presented in SQRT and incorporated in the APRRs to identify any corrective actions needed. A plan for implementing these additional reports (data collection method, procedures, etc.) will be developed by 15JUL2017 and implemented thereafter.

**OBSERVATIONS 6 - 9**

Pfizer and MMT senior management understand the significance of items raised in the 483 and fully appreciate the need for a comprehensive response and a robust corrective action plan to address these matters. MMT will engage SME's within the Pfizer / MMT / Industry network and experienced independent consultants with significant experience with medical device quality systems to develop a Compliance Action Plan ("CAP") that will identify corrective and preventative actions that will enhance our systems and processes. The CAP will focus on three primary areas for improvement, as identified in the observations and our own internal discussions:

- Design controls (including DHF)

- Complaint Investigations
- Acceptable Quality Limits (AQLs)

MMT is committed to addressing all the observations raised in the FDA 483. The responses include explanations of actions we have taken to date and additional corrective actions that are planned to fully address the FDA 483 observations to ensure full and sustainable compliance.

MMT acknowledges and takes very seriously FDA feedback. The comments shown below describe the corrective and preventive actions outlined in this document that MMT intends to complete to address FDA's observations 6 through 9.

- Review and enhance QSR procedures and systems to include evaluation of system level reliability and establish linkages between design inputs, design output, and design verification/validation.
- Document and justify through a risk assessment the system level reliability for EpiPen auto-injectors and essential functional characteristics and associate specifications.
- Modify functional specifications to single range specifications based on acceptable intended use.
- Apply a (b) (4) to determine sample size for demonstrating system level reliability in testing critical functional attributes.

In this section, we will repeat each observation verbatim and then provide MMT's response.

**OBSERVATION 6**

*Procedures for design input have not been adequately established. Specifically,*

**OBSERVATION 6A**

*The design inputs/requirements of the EpiPen, EpiPen Jr., and* (b) (4) *products are not appropriate for the intended use of the products in regards to the reliability of the delivery system. The reliability inputs/requirements of the device according to your PRD/TRD 16-001 Rev 1 do not include a system level reliability design input/requirement.*

**Response to Observation 6A**

Introduction

System level reliability is defined in the current design verification / process validation protocols for EpiPen products. The system reliability requirements are described below in the blueprint overview and demonstrate that the requirements are appropriate for intended use of the products. As further preventive action to further strengthen its design controls, MMT will evaluate its design input procedures for potential updates to include development of system level reliability.

The EpiPen auto-injector is a "one-shot" device to be used in emergency situations and requires a high level of reliability. The auto-injectors are transported and stored before the one time use and typically spend their life in dormant storage in a state of stand-by readiness. Individual

EpiPen auto-injectors cannot be 100% functionally tested prior to shipping because a successful test results in the destruction of the device. Determining the reliability of a "one-shot" device presents a unique challenge to the manufacturer due to the destructive nature of testing. Acceptance sampling is a statistical method used to predict the reliability (probability of success) by estimating an attribute of the population through a sample. Attribute sampling uses the binomial equation to test the hypothesis that a product has an acceptable defective rate at some acceptable level of risk. For "one-shot" devices, the object of sampling is to verify that when the device is called upon to function, the probability of success is satisfactory at some desired level of confidence. A reliability specification for a "one-shot" device must be achieved by setting a specification that is commensurate with the risk of device failure balanced with the sampling requirements to demonstrate reliability while achieving sufficient yield available to provide the end user with an accessible product.

MMT believes the current system level reliability specification of (b) (4)% is acceptable for intended use. This reliability of (b) (4)% exceeds the reliability requirements for delivered dose accuracy (i.e. 97.5%) as specified in ISO 11608 for a D2 auto-injector system.

The current design of the EpiPen and EpiPen Jr. auto-injectors was approved in 2009, as a supplement to the EpiPen NDA 019430 (S-049), prior to the Combination Product GMP Rule becoming final in 2013 and current standards and guidance being published. The (b) (4) The (b) (4) The AQLs for critical tests for the current NGA product were filed and approved by the agency in the EpiPen NDA 019430 and subsequent supplements; (b) (4) The supplements to the NDA for the NGA platform were approved by the agency with these AQLs and have been followed by MMT in the required product specifications. (b) (4) For EpiPen product these sampling plans (b) (4) i.e. the sampling plan requires (b) (4) critical defects or the batch will be rejected, regardless of AQL.

Product quality and reliability were designed into the EpiPen NGA platform through a series of development activities (in line with 21 CFR 820) and are ensured during production through a variety of process controls. Activities completed during development to ensure reliability included (b) (4) process development and qualification as well as functional qualification through a performance qualification protocol that included:

- All individual components are qualified to at least a (b) (4) cpk for all critical to function or indicative dimensions
- Testing to (b) (4)% reliability under nominal conditions
- Testing under a variety of pre-conditioning (b) (4) operation, (b) (4) operation, (b) (4), (b) (4) tests (b) (4) tests, (b) (4) testing, etc. based on ISO 11608 and MIL-STD-810 standards

The on-going production process controls to ensure quality and reliability include but are not limited to the following:

- All component production is governed by an approved Supplier Quality Plan
- 100% automated testing of key non-destructive sub-assembly features and functions as part of the automated assembly process for needle cover and Power Pak sub-assemblies at the supplier
- Functional release testing of sub-assemblies prior to release from supplier following ANSI/ASQ Z1.4
- Functional acceptance testing of sub-assemblies by MMT upon receipt of sub-assemblies from suppliers following ANSI/ASQ Z1.4
- 100% automated inspection and non-destructive testing of key features and functions of the finished product during automated inspection, testing, assembly, and packaging process
- 100% visual inspection including QA audit of the inspections and functional release testing of finished product with cumulative test results demonstrating reliability above specified reliability of (b) (4) %

Refer to section 3.2.P.3.3 Description of Manufacturing Process and Process Controls of the EpiPen NDA 019430 (b) (4) ) for more detailed information.

Risk Based Reliability

Reliability requirements must be set by considering the severity of potential harm to the patient if a failure were to occur. Severity of harm is categorized into three levels based on FDA guidance for industry titled *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions* issued 27DEC2016. The criticality of the risks resulting from an auto-injector functional failure is categorized in Table 1. Device reliability specifications are selected according to treatment and intended use of the product. A product that is used one or twice a week to provide chronic therapy for a non-life threatening condition may be classified as a major or minor risk level. EpiPen' s intended use and treatment is for an acute emergency, life-saving situation and has a risk ranking of critical.

**Table 1) Product risk ranking and corresponding reliability specification**

| Risk Ranking | Severity of Potential Harm | Reliability specification | Confidence Level |
|---|---|---|---|
| Critical | Device failure that creates a hazard that could result in a death or serious injury | (b) (4)% * | (b) (4)% |
| Major | Device failure that creates a hazard that could result in a non-serious adverse event including minor, temporary, or medically reversible adverse events | (b) (4)% | |
| Minor | Device failure may result in pain or discomfort or other inconvenience | (b) (4)% | |

* This reliability of (b) (4)% exceeds the reliability requirements for delivered dose accuracy as specified in ISO 11608 for a D2 auto-injector system.

To establish the reliability requirements specifically for an auto-injector, its function and usage have been analyzed to understand the ways in which the device can fail to perform properly. FMEAs, Fault Tree analysis, Risk analysis, Product and Technical Requirement Documents were reviewed for EpiPen. Reliability specification targets were selected accordingly.

Based on the main functions, the following key process output variables (KPOVs) were identified:

- Delivered Volume
- Extended Needle Length
- Dispense Time
- Activation Force
- Needle Cover Safety mechanism performance

The hazard analysis in Table 2 evaluates the consequences for these KPOVs.

**Table 2) Hazard analysis for KPOVs for EpiPen.**

| Function /KPOV | Hazard | Consequences | Risk |
|---|---|---|---|
| **Delivered volume** | Overdose | Dangerous adverse consequences, possible patient death. | Critical |
| | Under dose | Dangerous adverse consequences, possible patient death. | Critical |
| **Extended Needle Length** | Too deep | Potential bone strike | Major |
| | Too shallow | Potential reduced absorption rate (EpiPen is indicated subQ or IM) | Major |
| **Dispense Time** | Too Long | Under dose, if drug not delivered within specified hold time | Critical |
| **Activation Force** | Too High | Does not activate resulting in no drug delivered | Critical |
| **Safety mechanism** | Too low | Potential spontaneous activation resulting in no drug delivered to patient | Critical |
| | Needle stick injury if needle cover doesn't deploy | Injury to patient or user | Major |

**Reliability Verification Test Plan**

A design verification test plan was established to demonstrate the device functions and meets the specified reliability under a variety of conditions. Typical reliability tests and test conditions as performed for the NGA platform are listed in Table 3. ISO 11608 and MIL-STD-810 form the basis for test conditions which includes functional activation testing at typical use conditions and specific reliability testing under targeted stress levels to support potential misuse and conditions that auto-injectors may experience through the expected life. The highly accelerated stress test and accelerated aging study at the bottom of the list are new tests and consist of a sequence of tests related to expected stress conditions in the hands of users, followed by an activation test to verify the proper functionality of the device. Based on FDA feedback, as part of the system level reliability risk assessment MMT will evaluate [redacted (b) (4)] of auto-injectors to include in reliability testing. The system level reliability risk assessment will be completed by 31JUL2017.

**Table 3) Example of reliability tests by stress area**

| Stress area | Test | Test conditions |
|---|---|---|
| Functional activation | Functional testing at (b) (4) | (b) (4) |
| | (b) (4) operational range | |
| (b) (4) | (b) (4) operational range | |
| | (b) (4) | |
| | (b) (4) | |
| | (b) (4) Test - (b) (4) test, (b) (4) | |
| | (b) (4) Test - (b) (4) test, (b) (4) | |
| (b) (4) | (b) (4) | |
| | (b) (4) | |
| | (b) (4) | |
| (b) (4) | (b) (4) | |
| (b) (4) | (b) (4) | |
| | (b) (4) test | |
| **Testing under consideration** | | |
| (b) (4) | **Test** | **Test conditions** |
| (b) (4) | | |

* These tests have yet to be completed and the necessity will be considered as part of the risk assessment.

**Reliability Control Plan**

In addition to design verification testing, a sampling plan for on-going production release testing must be appropriate for the system level reliability specification. Table 4 below presents proposed AQLs for functional release testing that will demonstrate the specified reliability is met for individual lots. For critical defects, the sampling plan (b) (4), i.e. the sampling plan requires (b) (4) defects for failure to deliver, or the batch will be rejected, regardless of the AQL.

**Table 4) Examples of AQLs for Functional Release Testing Based on Product Criticality**

| Reliability Specification | Corresponding AQL | Number of Samples | Accept/Reject | Confidence Level for Reliability Specification |
|---|---|---|---|---|
| (b) (4)% | AQL (b) (4) | (b) (4) | (b) (4) | (b) (4)% confidence |
| (b) (4)% | AQL (b) (4) | | | % confidence |
| (b) (4)% | AQL (b) (4) | | | % confidence |

It should be noted that as subsequent lots pass functional testing the demonstrated reliability increases. For instance, after (b) (4) lots of EpiPen pass functional testing for the critical reliability of (b) (4) the resulting reliability estimation, based on (b) (4) samples with (b) (4) failures, demonstrates a higher level of reliability.

MMT firmly believes the current system level reliability is appropriate for intended use and the PRD/TRD 16-001 rev1, design inputs document, will be updated to include the system level reliability specification of (b) (4)%. This reliability of (b) (4)% exceeds the reliability requirements for delivered dose accuracy as specified in ISO 11608 for a D2 auto-injector system. The risk management file will be updated with a risk assessment performed by a cross-functional team, including Safety/Medical, to confirm essential attributes and their criticality based on severity of harm and intended use of the combination product. The PRD/TRD design inputs document will be reviewed to ensure completeness and that the inputs are written in a non- conflicting or ambiguous way.

MMT will take the preventive action to evaluate SOP-DVL-PRT-00002, *Design Inputs For New Products, Major Changes To Existing Products And Changes Affecting Product/User Interaction*, procedure for potential updates to include the development of a system level reliability and to ensure linkage to the design outputs. This procedure will be applied to all MMT products. The procedure will require the Design Input document, PRD/TRD, to include cross reference to the risk assessment and documentation supporting the individual design inputs. Training methodology using human performance tools to will be developed to assure adherence with the procedure. The preventive actions will be completed by 31JUL2017.

**OBSERVATIONS 6A1-6D**

Background

By way of background for Observations 6A1-6D, MMT would like to note that the AQLs for critical tests, as well as the functional attributes and ranges considered for critical test, for the current NGA product and (b) (4) product were filed and approved by the agency in the EpiPen NDA and subsequent supplements. The supplements to the NDA for the NGA platform were approved by the agency with both these AQLs and functional attributes and ranges, and have been followed by MMT in the required product specifications.

These same AQLs, as well as the functional attributes and ranges, were proposed and were applied to the (b) (4) product specifications, (b) (4) With regard to these products, for critical defects, the sampling plan (b) (4), i.e. the sampling plan requires (b) (4) defects for failure to deliver, or the batch will be rejected, regardless of the AQL.

**OBSERVATION 6A1**

*Your inputs/requirements list an AQL* (b) (4) *for critical tests, which equates to establishing a certain confidence of no more than* (b) (4) *failures per* (b) (4) *products.* (b) (4) *failures of delivered dose, or other critical tests, per* (b) (4) *EpiPen, EpiPen Jr., or* (b) (4) *products does not give assurance of the level of reliability commensurate with the risk of failure of a critical test as defined by your firm (e.g. delivered dose,* (b) (4) *, etc.).*

**Response to Observation 6A1**

The risk management file will be updated with a risk completed by 31JUL2017, performed by a cross-functional team including representatives from Safety /Medical/ Clinical groups, to document essential attributes and their criticality and rationale for design inputs. For those essential characteristics that are confirmed as critical in Table 2 Part 6A or modified per the safety/ medical risk assessment, (b) (4) will be eliminated and replaced with a (b) (4) based on acceptable use for all EpiPen products including the (b) (4) . The current AQL of (b) (4) will be changed to a (b) (4) AQL of (b) (4) for product release testing demonstrating system level reliability. (See Part 6A response Table 4.) Risk control within the supply chain will be evaluated to verify it supports the recommended system level reliability.

**OBSERVATION 6A2**

*Your pharmaceutical / drug delivery performance inputs/requirements list the inputs/requirements for certain essential performance inputs/requirements being specified to an AQL of* (b) (4)*, which establishes a certain confidence of no more than* (b) (4) *failures of an essential performance input/requirement, such as* (b) (4) *, per* (b) (4) *products.*

**Response to Observation 6A2**

The risk management file will be updated with a risk assessment completed by 31JUL2017, including representatives from Safety /Medical/ Clinical groups to document essential attributes and their criticality and rationale for design inputs. For those essential characteristics that are confirmed as critical in Table 2 Part 6a or modified per the safety/ medical risk assessment, (b) (4) will be eliminated and replaced with a (b) (4) based on acceptable use for all EpiPen products including (b) (4). The current AQL of (b) (4) will be changed to a (b) (4) AQL of (b) (4) for product release testing demonstrating system level reliability. (See Part 6A response Table 4.) Risk control within the supply chain control plan will be evaluated to verify it supports the recommended system level reliability.

**OBSERVATION 6A3**

*No rationale is provided for the acceptability of these design inputs/requirements based on the emergency use, life-saving intended use of the product.*

**Response to Observation 6A3**

Pfizer MMT Medical/ Clinical has approved the design inputs document as currently in place and Medical has reviewed and approved the Use FMEA as presented to the agency as part of the design validation, risk management file. The risk management file will be updated with a risk assessment completed by 31JUL2017, including representatives from Safety/Medical/Clinical, to document the rationale for the ranges of the essential performance inputs and their criticality/severity based on the emergency, life-saving intended use of the product. (See Part 6A response) The PRD/TRD design input document will be updated to include cross reference to the risk assessment and documentation supporting the risk assessment conclusions.

**OBSERVATION 6B**

*The design inputs/requirements of the EpiPen, EpiPen Jr., and* (b) (4) *are conflicting. In PRD/TRD 16-001 Rev 1 the design inputs/requirements related to the 'Pharmaceutical / drug delivery performance' of the EpiPen, EpiPen Jr., and* (b) (4) *have specifications that are outside of the principal design attributes listed. As an example, the principal design attribute for the EpiPen for dose volume is* (b) (4) *-* (b) (4) *mL. However, under input/requirement the delivered dose volume for the EpiPen is described as* (b) (4) *-* (b) (4) *mL @ AQL* (b) (4)*. Not less than* (b) (4) *or greater than* (b) (4) *mL at AQL* (b) (4)*'.*

**Response Observation 6B**

The PRD/TRD design inputs document will be reviewed to ensure completeness and that the inputs are not written in a conflicting or ambiguous manner. The design inputs document will be updated for consistency between the product requirements section and the technical requirements section. For those essential functional attributes that are confirmed critical through the risk assessment process, a single range specification, based on acceptable use, with a (b) (4) AQL applied for release testing will be instituted. (See Part 6A response for analysis)

**OBSERVATION 6C**

*The design inputs/requirements of the EpiPen, EpiPen Jr., and* (b) (4) *do not directly trace to a risk assessment of the product. It is unclear if the specifications listed under the 'Must' column of the document titled PRD/TRD 16-001 Rev1 are appropriate for the intended use of the device and the user/patient needs, especially considering that many of the specifications are split into different levels of acceptability based on the confidence of a sampling plan.*

**Response Observation 6C**

The risk management file will be updated with a risk assessment to be completed by 31JUL2017, including review by representatives from Safety/Medical/Clinical to document the rationale for the ranges of the essential performance inputs and their criticality based on the emergency, life-saving intended use of the product. MMT will update the PRD/TRD to trace the requirements to appropriate justifications and risk assessment. The design inputs document format will be revised to eliminate ambiguity between "Must" and "Want" design inputs. The "Wants" requirements of a PRD/TRD document will be removed from the document prior to finalizing design outputs such that design outputs can be traced directly to design input requirements.

**OBSERVATION 6D**

*Design inputs/requirement specifications of the EpiPen, EpiPen Jr., and* (b) (4) *utilize AQLs to describe the necessary confidence level associated with each range of a specification; however, AQLs do not consider the needs of the user/patient. As an example, in PRD/TRD 16-001 Rev 1 the* (b) (4) *input/requirement specification is described with two different AQLs for two ranges of values associated with* (b) (4) .

**Response to Observation 6D**

The risk management file will be updated with a risk assessment to be completed by 31JUL2017, by a cross-functional team including representatives from Safety/Medical/Clinical, to document the rationale for the ranges of the essential performance inputs and their criticality based on the emergency, life-saving intended use of the product. For those essential functional attributes as described in Table 2, part 6A a single range specification based on User/ Patient needs will be reassessed to determine an appropriate AQL or quality standard that sets a test sample size commensurate with demonstrating system level reliability. These values will be applied to all relevant documents and the necessary updates will be made.

**OBSERVATION 6E**

*Your firm has not established design inputs/requirements regarding the ability of the device to successfully inject through clothing as specified by the intended use of the product as defined by your firm's Injection Sites and Site Condition of the PRD/TRD 16-001 Rev 1 document.*

**Response to Observation 6E**

MMT has conducted multiple studies to demonstrate the ability of similar auto-injector designs to inject through multiple layers of clothing. These included tests of injectors having a similar functional design as the EpiPen auto-injector. The injectors tested used a similar glass cartridge and needle assembly, of (b) (4), with the same (b) (4) and the same (b) (4) in the firing mechanism. The auto-injectors were successfully fired through a layered combination of undergarments, multiple uniform layers, and heavy protective garments. Drug dispersion studies were also conducted with successful injection through denim cloth with NGA EpiPens and summarized in a published paper "*Comparison of drug delivery with autoinjector versus manual prefilled syringe and between three different autoinjector devices administered in pig thigh*". Post marketing surveillance has not identified any issues related to activation of the auto-injector through clothing.

In the design input document, PRD/TRD 16-001 Rev1, injection through clothing is a requirement included as part of the use specification. This will be added to the Technical Requirement section of the PRD/TRD design inputs document.

**OBSERVATION 7**

*Procedures for design output have not been adequately established. Specifically,*

**OBSERVATION 7A**

*Your firm has not established design outputs that allow an adequate evaluation of conformance to design input requirements. The design outputs as defined by your firm in the Design History File document titled DHF 17-001 Rev1.0 include batch record tests, controlled drawings, QC test reports, and SOPs that do not establish acceptance criteria for any system level reliability requirements after (b) (4) given the intended use of the product.*

**Response Observation 7A**

Historically system level reliability has been defined in design verification and functional qualification protocols and submitted with the NDA and have been submitted with the NGA supplement to the EpiPen NDA. As part of our corrective action the design inputs requirements of PRD/TRD 16-001 Rev 1,"Product and Technical Requirements Document "EpiPen Bitartrate Truject™ Next Generation Auto-injector" will be updated to include the system level reliability requirement of (b) (4) for essential performance requirements and (b) (4) This will be documented as a design output, in the engineering drawings:

8033035 rev A, NGA AUTO-INJECTOR ASSEMBLY, EPIPEN
8033036 rev A, NGA AUTO-INJECTOR ASSEMBLY, EPIPEN JR.
8033027 rev1, NGA 0.3mg AUTO-INJECTOR ASSEMBLY, (b) (4) PLUNGER
8033028 rev 1, NGA 0.15 mg AUTO-INJECTOR ASSEMBLY, (b) (4) PLUNGER

MMT will review the PRD/TRD, design inputs document, to ensure completeness and that the inputs and outputs are not written in a conflicting or ambiguous manner. Note that reliability specification (b) (4), i.e. the reliability specification will result in (b) (4) critical defects regardless of sample size tested.

MMT will take the preventive action to evaluate SOP-DVL-PRT-00003, *Design Outputs for New Products, Major Changes to Existing Products and Changes Affecting Product /User Interaction,* for linking design outputs to the design input requirements and the procedure will be updated as required to include a cross referencing of design output conformance to design inputs. Training methodology using human performance tools will be used to assure adherence with the updated procedure. The preventive actions will be completed by 31JUL2017.

**OBSERVATION 7B**

*The design outputs acceptance criteria do not reflect the risk associated with the failure of the specifications. The design output documents for the design input requirements allow for failures of the design attributes. As an example, it is acceptable for failures of 'major' functional requirements to occur such as delivered volume outside of the specification of* (b) (4) - (b) (4) *mL.*

**Response to Observation 7B**

The functional attributes and ranges considered for critical tests for the current NGA product and applied to the (b) (4) product were filed by MMT and approved by the agency in the EpiPen NDA and subsequent supplements. The supplements to the NDA for the NGA platform were approved by the agency with these functional attributes and ranges and have been followed by MMT in the required product specifications. For critical defects, the sampling plan (b) (4) i.e. the sampling plan requires (b) (4) defects for failure to deliver, or the batch will be rejected, regardless of the sample size. These same attributes were proposed and were applied as the product specification for (b) (4), which has the same emergency use, life-saving intended use as the NGA EpiPen.

The design outputs will be reviewed to ensure completeness. The risk management file will be updated with a risk assessment completed by 31JUL2017, by a cross-functional team including representatives from Safety/Medical/Clinical, to document the rationale for the ranges of the essential performance inputs and their criticality based on the emergency, life-saving intended use of the product. For those essential functional attributes as described in Table 2, part 6A a single range specification based on User/ Patient needs will be assessed to determine an appropriate AQL or quality standard that sets a test sample size commensurate with demonstrating system level reliability. These requirements will be reflected in both the design inputs and the design outputs.

**OBSERVATION 8**

*Procedures for design verification have not been adequately established. Specifically,*

**OBSERVATION 8A**

*Your firm has not developed design verification testing that adequately tests that the design outputs meet the design inputs, specifically in regards to the reliability of the device at the end of the labeled date of expiry. No verification testing exists that is reflective of the design input requirement that the drug delivery performance must be acceptable at the end of product expiry.*

**Response to Observation 8A**

Annual stability testing is performed and includes functional testing through the end of product expiry of the NGA product. Post marketing surveillance indicates there are no issues of shelf life affecting the functional reliability of the auto-injector.

Corrective measures will include executing a study with full functional system level reliability testing including (b) (4) of auto-injectors, if required, using auto-injectors produced as part of submission batches and (b) (4) for (b) (4) years. This testing will be completed by 30SEP2017.

Preventive action will include requiring functional system level reliability testing of the auto-injector device at end of product expiry, (b) (4) stability for future submission lots. For submissions made at less than full product expiry dating with (b) (4) stability testing, a system level reliability test following (b) (4) (b) (4) year equivalent) may be included.

Design input and verification procedures will be updated for these considerations of system level reliability at end of expiry. MMT will take the preventive action to evaluate the design control procedures for needed updates to ensure linkage of design verification requirements to the design input and outputs. Training methodology using human performance tools to will be used to assure adherence with the procedure. The preventive actions will be completed by 31JUL2017.

**OBSERVATION 8B**

*The test methods for design verification testing are inadequate.* (b) (4) *of the final product is not done* (b) (4) *prior to functional verification testing according to your document PR-14719 titled 'Final Report - Component and Functional Qualification of the NGA EpiPen Sr. Auto-Injector using* (b) (4) *Plungers from* (b) (4) *' for the* (b) (4) *. The same is true for the completed verification testing of the EpiPen and EpiPen Jr. products.*

**Response to Observation 8B**

MMT has based (b) (4) of the combination product device, prior to design verification tests and commercial process validation, on the Mil-Std 810 and ISO 11608 requirements as

recognized by the agency, as well as FDA guidance "Technical Considerations for pen, Jet, and related injectors intended for use with drugs and biological products", tailored for each specific auto-injector product. These standards have not had (b) (4) as a requirement. MMT will develop through the risk assessment process the (b) (4) requirements for design verification and commercial process validation functional testing to be included as a component of the design verification and design validation plans. PRD/TRD 16-001 rev1, design inputs, will be updated to include requirements for (b) (4) testing. The Design Control procedures will be updated to require evaluation of (b) (4) (See Table 2 Observation 6A for examples). MMT will take the preventive action to evaluate the design control procedures for needed updates to ensure linkage of design verification requirements to the design input and outputs. Training methodology using human performance tools to will be developed to assure adherence with the procedure. The preventive actions will be completed by 31JUL2017.

**OBSERVATION 8C**

*Verification testing demonstrated failures of design requirements according to PR-14719; however, these failures were deemed acceptable within the test report conclusions. Your firm confirmed that the same test failures would not be acceptable during lot release testing and would trigger the initiation of an investigation. For example, in PR-14719 one unit of the* (b) (4) *units tested during the* (b) (4) *test was noted to have a delivered volume of* (b) (4) *ml, which is outside of the delivered volume specification of* (b) (4) - (b) (4) *ml. The conclusion of the test was that it was acceptable to have up to* (b) (4) *delivered volume failures per the specification of* (b) (4) - (b) (4) *ml and still pass the acceptance criteria.*

**Response to Observation 8C**

The functional attributes and ranges considered for critical tests for the current NGA product and applied to the (b) (4) product were filed by MMT and approved by the agency in the EpiPen NDA and subsequent supplements. The specification for delivered volume has a critical range of (b) (4) mL – (b) (4) mL. The supplements to the NDA for the NGA platform were approved by the agency with these functional attributes and ranges and have been followed by MMT in the required product specifications and are reflected in the verification protocols. Note that these specifications (b) (4), i.e. the plan results in (b) (4) critical defects regardless of sample size. These same attributes were (b) (4), which has the (b) (4).

As a corrective action, the design inputs and outputs will be reviewed to ensure completeness. The risk management file will be updated with a risk assessment completed by 31JUL2017. For those essential functional attributes as design inputs and outputs that are confirmed critical through the risk assessment process, a single range specification with a (b) (4) AQL for determination of sample size will be applied for release testing reflecting system level reliability. (b) (4) for critical functional attributes. (See Table 4, Part 6A response) Corrective measures will also include executing a design verification study with full functional system level reliability testing including (b) (4) of auto-injectors,

if required, using auto-injectors produced as part of submission batches and (b) (4) for [b] years.

MMT will take the preventive action to evaluate SOP- DVL-PRT-00003, *Design Outputs for New Products, Major Changes to Existing Products and Changes Affecting Product /User Interaction*, for linking design outputs to the design input requirements and the procedure will be updated to include evaluations of design output conformance to design inputs. Training methodology using human performance tools will be used to assure adherence with the procedure. The preventive actions will be completed by 31JUL2017.

**OBSERVATION 8D**

*Essential performance requirements such as (b) (4), activation force, dispensing time, and dispensing volume are listed to have a reliability of (b) (4)% in PR-14719 which is not commensurate with the listed design input requirements of PRD/TRD 16-001 Rev 1, nor is it commensurate with the risk associated with the intended use of the product.*

**Response to Observation 8D**

Historically system level reliability has been defined in design verification and functional qualification protocols and submitted with the NDA and have been submitted with the NGA supplement to the EpiPen NDA. As part of our corrective action the design inputs requirements of PRD/TRD 16-001 Rev 1,"Product and Technical Requirements Document " (b) (4) will be updated to include the system level reliability requirement of (b) (4)% for essential performance requirements and reasonably (b) (4) (See Response Part 6A.) This will be documented as a design output, in the engineering drawings:

8033035 rev A, NGA AUTO-INJECTOR ASSEMBLY, EPIPEN
8033036 rev A, NGA AUTO-INJECTOR ASSEMBLY, EPIPEN JR.
8033027 rev 1, NGA 0.3mg AUTO-INJECTOR ASSEMBLY, (b) (4) PLUNGER
8033028 rev 1, NGA 0.15 mg AUTO-INJECTOR ASSEMBLY, (b) (4) PLUNGER

and will be updated to include the reliability requirement of (b) (4)%. Reliability will then be defined in the design output and used to determine design verification requirements. MMT will review the PRD/TRD, design inputs document, to ensure completeness and that the inputs are not conflicting or ambiguous. Note that the reliability specification (b) (4) i.e. the reliability specification results in (b) (4) critical defects regardless of sample size tested.

MMT will take the preventive action to evaluate the design verification and validation procedure SOP- DVL-PRT-00004, *Design Verification and Validation for New Products, Major Changes to Existing Products and Changes Affecting Product /User Interaction*, for linking design verification requirements to the design input and output requirements. The procedure will be updated and training methodology using human performance tools will be used to assure adherence with the procedure. The preventive actions will be completed by 31JUL2017.

**OBSERVATION 9**

*Procedures for design validation have not been adequately established. Specifically,*

**OBSERVATION 9A**

*Your firm has not completed any validation testing of the design of the device in order to ensure that the devices conform to the defined intended uses. No validation testing was conducted to establish the device specifications conform with the intended use of the product to a degree of reliability commensurate with the risk associated with the device (e.g. no failure rate at product expiry has been established through design validation). Actual or simulated use conditions (e.g. activation orientation, environmental temperature, injection through clothing, etc.) are not part of the design validation plan. Validation testing has not been conducted on initial production units, lots, or batches for the EpiPen, EpiPen Jr., or* (b) (4) *products.*

**Response to Observation 9A**

Design verification and design validation effectively combine to qualify a new product for its intended use. MMT understands that design verification testing is part of and supports design validation. MMT has conducted testing with simulated use conditions identified in this observation as design verification tests that do not require testing in the hand of users. Design verification/process qualification testing was completed for the NGA platform in 2009 and included (b) (4) for potential patient misuse beyond the labeled storage conditions and environmental stress conditions. Design verification/process qualification for (b) (4) was completed in 2015. Simulated use conditions for functional aspects such as activation orientation, environmental temperature, injection through clothing (see response for Observation 6E) have been performed and support design verification. For reliability at expiry see response for Observation 8A. See Observation 9B for design validation.

**OBSERVATION 9B**

*No validation testing has been conducted on the user interface of the EpiPen, EpiPen Jr., or* (b) (4) *products.*

**Response to Observation 9B**

The EpiPen and EpiPen Jr. products were approved in 2009, as a supplement to the EpiPen NDA, prior to the Combination Rule becoming final in 2013 and current standards and guidance being published, e.g. (standard IEC 62366-1:2015 published in 2015 and FDA guidance Applying Human Factors and Usability Engineering to Medical Devices published 03FEB2016). While some basic formative human factors engineering was conducted during the design of the NGA auto-injector, these legacy products were not required to be subjected to a simulated use design validation process to current, contemporary standards. Instead, design validation, or usability engineering, for the EpiPen and EpiPen Jr. products followed IEC 62366-1:2015 Annex C; Evaluation of a User Interface of Unknown Provenance. This standard is fully recognized in its entirety by FDA. Annex C states "*This annex was created in recognition of the fact that many MANUFACTURERS will be interested in applying the tools defined in this standard to*

*USER INTERFACES or parts of USER INTERFACES that* ***have already been commercialized*** *prior to the publication of this edition of this standard. Such USER INTERFACES or parts of USER INTERFACES were not developed using the PROCESSES of IEC 62366-1 and as a result are of unknown provenance with respect to these PROCESSES. Since this standard focuses on USABILITY ENGINEERING as part of the product development PROCESS, it was determined that an appropriately scaled (as described in 4.3) and alternative PROCESS should be developed to cover these USER INTERFACES or parts of USER INTERFACES of unknown provenance.*" From annex C the Usability Engineering Process for User Interface of Unknown Provenance requires the following:

- The manufacturer shall establish a Use Specification.
- The manufacturer shall review available post-production information including complaints and field reports for incidents or near incidents.
- The manufacturer shall review the risk analysis and ensure that the hazards and hazardous situations associated with usability have been identified and documented.
- The manufacturer shall verify and document that adequate risk control measures have been implemented for all identified hazards and hazardous situations and that all risks are reduced to an acceptable level as indicated by the risk assessment.
- The manufacturer shall evaluate the overall residual risk and document the result in either the usability engineering file or the risk management file.

MMT has conducted all of these activities and documented the results in a usability engineering file for the EpiPen product line.

The (b) (4) auto-injector uses the same device as the EpiPen and EpiPen Jr. (b) (4) and no changes to the device-user interface were made or planned. In adopting the same platform with the same functional specifications for the same users, same intended use, and the same use environment, the (b) (4) followed the usability engineering process from IEC 62366-1:2015 Annex C, Example 1 which states "*Example 1 For an unchanged legacy USER INTERFACE that was designed and developed prior to the publication of IEC 62366-1:—, the USER INTERFACE is evaluated using this annex for determining conformance to this standard.*" A simulated use study has been determined to be of limited value due to the post-marketing surveillance data available for the EpiPen NGA product which represents real-world results across a wide variety of end users and use environments with much higher numbers of users than would normally be achieved in a simulated-use design validation study.

**OBSERVATION 9C**

*No risk analysis was conducted for the 'basic unit' subassembly of the EpiPen product line. Also, the document titled 'NGA Truject Autoinjector Risk Assessment' reference 8637935n FMEA Report has not been reviewed since its issuance in 2009.*

**Response to Observation 9C**

As stated during the inspection, the basic unit dFMEA was in draft at time of inspection. The basic unit dFMEA will be approved by 31MAY2017. The basic unit dFMEA will be merged with the auto-injector dFMEA into a single document to consider the entire combination product device. The dFMEA reference 867935n "NGA Truject Auto-injector Risk Assessment "will be reviewed at a minimum of annually as part of the APRR. The dFMEA risk assessment will be incorporated into the plant quality systems including (b) (4), Complaints, Change Control and for risk management.

**OBSERVATION 10**

*Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity. Specifically, we witnessed functionality testing of EpiPen and observed the following:*

**OBSERVATION 10A**

*The lot release test fixtures, which are used to perform the functionality testing of the final finished product, does not include assurance that all test surfaces are level. We also observed that the employee conducting the testing did not* (b) (4) *to ensure that the* (b) (4) *was not affected by the environment during testing. The* (b) (4) *the products during testing appeared damaged and currently there is no standard operating procedure for conducting preventive maintenance on this equipment.*

**Response to Observation 10A**

**Leveling of Test Stand Instruments**

The Functionality Test Stands are each composed of (b) (4) instruments to conduct the Activation Force, Delivered Volume, Dispense Time, and (b) (4) tests. The (b) (4) instruments are a (b) (4) A review of the manufacturer's documentation for (b) (4) devices determined that the (b) (4) is the only device that requires leveling and that this task can be performed separately from the other instruments. The requirement to level the (b) (4) before use by using the (b) (4) is already included in both procedures that address the Functionality Test Stand (b) (4), SOP-QLC-SQC-00307, *Functionality Testing of NGA Auto-Injectors,* and SOP-QLC-SQC-00394, *Functionality Testing of Auto-Injectors.*

The other (b) (4) instruments in the Functionality Test Stands have the following requirements for setup, which are stated in the manufacturer instructions and in the MMT procedures.

- The (b) (4) requires setting the (b) (4) prior to testing.
- The (b) (4) requires the inspection of the (b) (4) before operation; specifies a (b) (4); and notes that the equipment must be (b) (4) prior to testing.
- The (b) (4) requires setting the display to (b) (4) prior to testing.

(b) (4)

Since the conclusion of the inspection, MMT conducted an evaluation of two years (2015 and 2016) of the Delivered Volume test data. The process capability index (PpK) was calculated for the Delivered Volume test for EpiPen, EpiPen Jr. and ATNAA finished products. The PpK results were (b) (4) and (b) (4), respectively. These results are indicative of a process that is highly capable of producing products that consistently meet the specifications, with no indication of an impact from an (b) (4).

Nevertheless, we recognize the importance of controlling for potential variables in our tests, and procedures SOP-QLC-SQC-00307 and SOP-QLC-SQC-00394 will be revised by 30APR2017 to require that the (b) (4). Colleagues will be re-trained on the revised procedure, which will also include re-training on the requirement to level the (b) (4).

(b) (4) **Units During Testing**

The purpose of the (b) (4) is to (b) (4) by the (b) (4). A new procedure to address preventive maintenance for the Functionality Test Stands and the (b) (4) will be effective by 30APR2017. (b) (4) by 15JUL2017 to replace the ones that appear to be more used. The preventative maintenance procedures for all other equipment in the lab will be confirmed by 30APR2017.

**OBSERVATION 10B**

*We observed that drug product was accumulated on the* (b) (4). *We observed that the drug product inside the* (b) (4) *tool from previous testing can be transferred to the final finished product's* (b) (4) *after dispensing the drug product and prior to weighing the unit for the delivered dose measurement.*

**Response to Observation 10B**

Before responding to this finding, it should be noted that because this is destructive testing, none of the samples are returned to the lot for distribution. Since the conclusion of the inspection, MMT conducted an evaluation of two years (2015 and 2016) of the Delivered Volume test data. The process capability index (PpK) was calculated for the Delivered Volume test for EpiPen,

EpiPen Jr. and ATNAA finished products. The PpK results were (b) (4) and (b) (4), respectively. These results are indicative of a process that is highly capable of producing products that consistently meet the specifications, with no indication of an impact from intermittent carryover.

To prevent any potential for intermittent carryover, procedures SOP-QLC-SQC-00307, *Functionality Testing of NGA Auto-Injectors*, and SOP-QLC-SQC-00394, *Functionality Testing of Auto-Injectors*, will be enhanced to provide specific instructions for the (b) (4) , and (b) (4) the performance of the test by 30APR2017.

**OBSERVATION 10C**

*(b) (4) entry of (b) (4) and dispensed time relies on the operator to read the (b) (4) from d(b) (4) whereby the measurement of (b) (4) occurs (b) (4) of the device occurs.*

**Response to Observation 10C**

Since the conclusion of the inspection, Pfizer conducted an evaluation of two years (2015 and 2016) of the (b) (4) test data. The process capability index (PpK) was calculated for the (b) (4) test for EpiPen, EpiPen Jr. and ATNAA finished products. The PpK results were (b) (4), and (b) (4), respectively. These results are indicative of a process that is capable of producing products that consistently meet the specifications.

Procedures SOP-QLC-SQC-00307, *Functionality Testing of NGA Auto-Injectors*, and SOP-QLC-SQC-00394, *Functionality Testing of Auto-Injectors*, will be enhanced to provide specific instructions for the proper technique to (b) (4) and the measurement reading process. Visual aids will be added to the above procedures to ensure consistency of practices for the (b) (4) test execution and data recording. The additional detail will describe what types of readings the operator can expect to see on the (b) (4) and how (b) (4) .

**OBSERVATION 10D**

*Measurement results can be altered if a (b) (4) applied different forces to measurement tools. For example, the (b) (4) could be increased by applying more force to the device while (b) (4) measurement tool.*

**Response to Observation 10D**

The Functionality Test Stand is composed of (b) (4) instruments to conduct the (b) (4), Delivered Volume, (b) (4) and (b) (4) . The (b) (4) instruments are the (b) (4) ). The

only instrument that requires the use of (b) (4) is the (b) (4) measurement tool.

Procedure SOP-QLC-SQC-00331, (b) (4), defines the steps for the proper and consistent measurement of (b) (4). The procedure states to (b) (4) [redacted] ". The (b) (4) up to (b) (4) and (b) (4) since the (b) (4) of the (b) (4). The (b) (4) is reported to (b) (4) by the data collection system, and the product specification is in whole numbers. Therefore, any additional (b) (4) could not impact the final recorded value.

As noted above, since the conclusion of the inspection, MMT has conducted an evaluation of two years (2015 and 2016) of the (b) (4) test data. The process capability index (PpK) was calculated for the (b) (4) test for EpiPen, EpiPen Jr. and ATNAA finished products. The PpK results were (b) (4) and (b) (4), respectively. These results are indicative of a process that is highly capable of producing products that consistently meet the specifications.

MMT will evaluate the potential to modify the current (b) (4) to include a guide to keep the (b) (4) during the test. This would minimize the need to (b) (4) [redacted]. This evaluation will be completed by 30SEP2017.

**OBSERVATION 10E**

*There have been no studies conducted to establish inter-operator and inter-test stand variation of the functional test results. Currently, your firm has (b) (4) and up to (b) (4) operators who are trained to conduct these tests.*

**Response to Observations 10E**

A statistical study will be completed to evaluate inter-operator and inter-test stand variability for the functionality release testing for ATNAA and EpiPen by 15MAY2017. Data has been collected for this study. Action items will be established if any statistical differences are identified.

**OBSERVATION 10F**

*The operator conducting functional testing on a production lot of final finished product was not listed as an operator trained to complete the functionality testing of NGA Auto-injectors or Autoinjectors according to your firm's records in document SOP-QLC-SQC-00307 & 00394. Additionally, the same operator is not included in the training record for conducting testing of Power Pak.*

**Response to Observation 10F**

A Manufacturing Investigation Report (QAR PR 28624) was issued on 24FEB2017 to investigate that a QC Laboratory Analyst was not listed as trained on SOP-QLC-SQC-00307 and SOP-QLC-SQC-00394. The investigation revealed that the QC Laboratory Analyst was trained on the effective version of SOP-QLC-SQC-00394 (version 11.0) and on the effective version of SOP-QLC-SQC-00309 (version 10.0), *Testing of NGA* (b) (4) *Assembly*. However, it was verified that the QC Laboratory Analyst was not trained on the effective version of SOP-QLC-SQC-00307, but was trained on a previous version, version 17.0.

To determine the quality impact of this training gap, a review of the changes on SOP-QLC-SQC-00307 from version 17.0 to version 19.0 was performed. The review determined that none of the changes had impact to the validity of the data collected.

The changes related to version 18.0 are detailed below:

1. Add a new form reference.
2. Delete reference to an alternative (b) (4) no longer in use.
3. Include a verification that the (b) (4) is clean and free of debris, so that dispensed drug is not (b) (4), causing artificially (b) (4) Data generated by this QC Laboratory Analyst was reviewed and there was no high out of trend dispense times found.
4. Include a note related to a specific model of test stand.

For version 19.0, all changes were editorial changes (does not add, delete or change tasks) and did not modify the substantive practices set forth in version 17.0.

MMT concluded the training oversight did not impact the inspector's work product.

A review of the Functionality test data from 28MAR2016 (effective date for version 18.0) to 24FEB2017 (date of discovery) generated by the QC Laboratory Analyst identified during the inspection was conducted. No LIR (Laboratory Investigation Record) was identified that could be associated with failure to properly follow SOP-QLC-SQC-00307.

A review of the training process was performed in order to determine the root cause for this event. The investigation identified that the correct curriculum was not added to the QC Laboratory Analyst's training profile when he was transferred from the Production Department to the Quality Control Devices Laboratory. Since the Functionality Testing curriculum had not

been assigned, revisions to SOP-QLC-SQC-00307 did not signal the QC Laboratory Analyst to train.

The investigation concluded that assignable cause for this event is human error. The correct curriculum was not added to the QC Laboratory Analyst training profile when he was transferred from another area.

The following corrective actions were implemented at the time of the inspection:

1. The QC Laboratory Analyst involved in this event was trained on the current version of SOP-QLC-SQC-00307 on 24FEB2017. The analyst's curriculum was also updated.
2. A review of all QC Laboratory Analysts on 24FEB2017 confirmed that all analysts who perform Functionality testing were assigned the correct Functionality testing curriculum.

In addition, a process has been developed for the (b) (4) Administrators to prompt and follow up with managers to create/modify curricula for new employees, new contingent staff, or staff with job assignment changes. This process is already in place, but will be formally defined in a new (b) (4) procedure. The new procedure will be created by 30JUN2017.

Finally, all MMT curricula and curricula assignments for all colleagues will be reviewed by the responsible area manager or their designee by 31AUG2017 to ensure assignments are correct and complete. This review will be facilitated by Training Systems and area Training staff and formally documented according to SOP-TRN-GEN-00044, *Curricula Development and Revision at MMT*; curricula reviews will be completed annually thereafter.

**OBSERVATION 10G**

*There is no risk assessment, failure mode analysis, or determination of analytical variation conducted for the functional lot release test procedure and testing process.*

**Response to Observations 10G**

A FMEA will be completed to identify and prioritize potential failure modes in the functional lot release test procedures and testing process. A plan to implement mitigating actions for any failure modes with unacceptable risk priority numbers will be approved by 15JUN2017.

**OBSERVATION 11**

*The quality control unit lacks the responsibility and authority to approve and reject all components, drug product containers, closures, in process materials, packaging material and drug products. Specifically, Quality Assurance lacked a sufficient response to the positive sterility test of EpiPen (Epinephrine Injection, 0.3 mg) Lot 7GM063 that occurred on Friday 17 FEB 2017. The microorganism found was Bacillus cereus, a spore-former. For example, as of Thursday 24 FEB 2017:*

**Response to Observation 11**

The Quality Assurance unit has the responsibility and authority for lot release as defined in SOP-QLA-MQA-00600, *Batch Record Audit and Quality Assurance Product Disposition,* and SOP-QLA-MQA-00750, *Quarantine/Rejection of Materials*. Following the detection of turbidity in the (b) (4) read of the sterility test of EpiPen lot 7GM063 on 17FEB2017, Quality Operations (QO) immediately initiated a comprehensive, cross-functional investigation. The actions taken by QO demonstrate a robust response and include the following:

- Microbiology laboratory investigation LIR PR 28483 was opened 17FEB2017.
- A Quality Notification Report (QNR 2017-042) was initiated by Microbiology on Friday, 17FEB2017. The Site QO Leader (SQOL) completed the remaining sections of the QNR on 20FEB2017 and 21FEB2017 (Monday and Tuesday during the FDA audit), providing direction on information needed along with an evaluation concluding that there was potential quality impact. The evaluation also called for the filing of an NDA FAR.
- The VP of Aseptic QO was notified on 17FEB2017 in accordance with SOP QLA-MQA-00004, *Notification to Management*.
- A cross-functional investigation team was convened by QO on 18FEB2017. Team meetings continued daily through 26FEB2017, then as required until 27MAR2017. Team members included Quality, Production, Operational Excellence, Microbiology, corporate Microbiology and Aseptic Support, Compliance, and Environmental Control.
- As a precaution, Room (b) (4) (b) (4) insertion for EpiPen products), Room (b) (4) (filtration), and Room (b) (4) (EpiPen filling) were sanitized with (b) (4) (sanitizing agent) and (b) (4) (sporicidal) on 17FEB2017 and 18FEB2017. During this time, production was halted.
- Manufacturing Investigation Report QAR PR 28520 was opened 19FEB2017. The information in the QAR regarding impact to lot 7GM063 was expanded on 27FEB2017 to include all products and lot numbers for all lots produced since the last successful media fills, all of which were still within the control of MMT. The last successful media fill for ATNAA was filled (b) (4) and for EpiPen it was filled (b) (4).
- An Initial FAR was timely submitted to FDA on 23FEB2017.

The laboratory investigation, which was opened 17FEB2017, included a review of the sterility testing (b) (4) testing, the (b) (4) testing, the identity of the sterility test failure micro-organism, and the integrity of the (b) (4) from the units tested for sterility. This investigation also requested additional environmental monitoring of the testing supplies used in the failed sterility test and the testing (b) (4).

The Manufacturing Investigation Report initiated on 19FEB2017 examined the following:

- A review of the product flow process, cleaning records, sterilization records, sanitization records, formulation records, filling records, training records, (b) (4) testing, and HEPA certification testing.
- Historical review of media fills from 2017 to 2014 in the EpiPen filling line shows (b) (4) media fills were completed totaling (b) (4) units, all of which were negative for growth.
- A new media fill was requested and later run on 06MAR2017, which resulted in 0 positive units.

- As documented in the table below, the Environmental Monitoring Action Level Excursion for personnel and Room (b) (4) (EpiPen filling room) Grade A/B areas for 2015, 2016 and Jan/Feb 2017 is well below (b) (4) %. Passive air samples tested during this same time period show no actionable excursions.

| Sample | Year | Number of Action Level Excursions | Total Number of Samples | Action Level Excursion % |
|---|---|---|---|---|
| Personnel | 2015 | (b) (4) | (b) (4) | (b) (4) |
| | 2016 | | | |
| | Jan/Feb 2017 | | | |
| Room (b) (4) Grade A | 2015 | | | |
| | 2016 | | | |
| | Jan/Feb 2017 | | | |
| Room (b) (4) Grade B | 2015 | | | |
| | 2016 | | | |
| | Jan/Feb 2017 | | | |

**OBSERVATION 11A**

(b) (4) *batch operations continued on the Epinephrine line and other lines, with no extra controls mandated by QA to increase scrutiny of the aseptic processing operation.*

**Response to Observation 11A**

Following the detection of turbidity in the (b) (4) read of the sterility test of EpiPen lot 7GM063 on 17FEB2017, Quality Operations immediately requested suspension of EpiPen filling production once the lots in progress were complete. QO also specified that a sanitization with a (b) (4) and a (b) (4) sporicidal disinfection be performed in the rooms where the EpiPen product is filtered / filled. This disinfection took place on 17FEB2017 and 18FEB2017, prior to resumption of production. During this time, production was halted and no batches were released.

Also on 17FEB2017, QO Aseptic Observers on the filling lines were informed of the sterility failure so they could be vigilant for any aseptic process deviation.

On 18FEB2017, as noted above, QO immediately responded and managed a comprehensive, cross-functional investigation. Throughout the investigation no potential root cause in manufacturing was identified that would warrant additional controls other than all of the procedural controls already in place, e.g. Aseptic Observers and Floor Quality Operations.

**OBSERVATION 11B**

*Quality Assurance did not mandate a temporary suspension of batch release while the scope and possible cause of a sterility failure was being investigated.*

**Response to Observation 11B**

When QAR PR 28520 was opened on 19FEB2017, only lot 7GM063 was listed in the investigation report. On 27FEB2017, the listing of lots was updated to include all of the lots produced since the last successful media fill (all within MMT control). The lot release process for all products had been suspended prior to 17FEB2017 when the sterility failure was reported, due to a pending change control for the (b) (4) in the filtration suite. Therefore, there was no possibility to release any of the lots tied to the sterility investigation during the time period between 19FEB2017 and 27FEB2017.

Product manufacturing continued, as the sterility investigation progressed and the lot numbers for new batches produced were added to QAR PR 28520 as these batches were manufactured, to prevent product release. No batches were released until the QAR was approved by QA.

**OBSERVATION 11C**

*Your procedure SOP-LAB-MIC-00416 Investigation of a Sterility Test Positive, Tested in the* (b) (4)*, Version 9.0, only requires an evaluation of whether* (b) (4) *lots and* (b) (4) *" should be rejected, rather than evaluating if a larger issue exists on the line that could have broader scope. There is no requirement that your firm considers whether other lots manufactured on the line and in the facility may have been affected by the route of contamination.*

**Response to Observation 11C**

Laboratory SOP-LAB-MIC-00416, *Investigation of a Sterility Test Positive, Tested in the* (b) (4), requires an evaluation of (b) (4) lots and (b) (4) as part of the lab investigation when a sterility test positive is found. However, this is not the only procedure that governs investigations.

As a more general directive, all investigations must follow SOP-QLA-MQA-00720, *Event and Deviation Reporting (ER & QAR).* This procedure requires the evaluation of all potentially associated lots to define the scope of an incident, as well as to determine product impact. QA is required to provide a list of potential batches, material, areas, equipment, processes, and/or systems that could be affected by an event. As required by this procedure, all lots manufactured at the MMT facility were included in the scope of the investigation.

In short, QA followed procedures in this instance and exercised its clear authority to stop release of the implicated lots until it had completed its investigation. The Observation suggests that QA either lacked, or failed to exercise, appropriate authority to respond to the situation. In fact, QA responded immediately and took appropriate steps to interrupt production and evaluate the product impact. In response to this Observation, SOP-LAB-MIC-00416 will be revised by 30JUN2017 to also include this same holistic review of all lots that could be in scope of a sterility test failure, in accordance with SOP-QLA-MQA-00720.

**OBSERVATION 12**

*Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed. Specifically,*

**OBSERVATION 12A**

*We observed breaches in aseptic technique on the Epinephrine and ATNAA/DuoDote lines. For example:*

**Response to Observation 12A**

The MMT Brentwood site has a comprehensive program to train, qualify and monitor colleagues working in the Aseptic Processing Area (APA) on aseptic technique.
APA personnel and APA support personnel who work in Grade A/B production areas must successfully complete Aseptic Qualification Training to gain access to the APA and independently perform APA job functions. The Aseptic Qualification Training Program includes the following topics:

- Overview of aseptic operations and the critical nature of this work
- Demonstration of competency for aseptic gown practices and certification that includes (b) (4) gown sampling
- APA personnel conduct, practices, and hygiene
- Aseptic techniques
- (b) (4) and sources of contamination including bacterial endotoxin
- Viable and non-viable particulates
- Environmental control program including disinfection, decontamination, and sterilization of materials
- Preventing contamination of sterile equipment, containers, closures, in-process materials, and intermediates
- Prevention of disruption of unidirectional airflow
- Demonstration of competency for moving material into the APA through equipment airlocks
- Skill based training for specific job function requirements
- Participation in a successful aseptic processing simulation including performance of predefined interventions

To maintain certification, employees must complete initial qualification and (b) (4) certification training requirements. Employees are also required to complete (b) (4) results that exceed action limits. Training requirements are recorded and tracked in the site (b) (4) that is used to monitor the training status and schedule training to maintain certification.

Manufacturing Quality Assurance (MQA) colleagues are responsible for ensuring that APA personnel are appropriately gowned and practice good aseptic technique. There is also an Aseptic Specialist who supports aseptic operations in the Grade A, B, and C classified areas such as Filling, Formulation and Clean & Prep. In this role, the Specialists conduct periodic audits of

aseptic practices and behaviors in collaboration with Management and QA. They serve as an ongoing technical resource to aseptic operations, overseeing that production is manufactured with good aseptic behaviors and practices. The Production Aseptic Specialist is more extensively trained in microbiology, has prior experience in aseptic manufacturing, and has participated in Pfizer cross-site training.

**OBSERVATION 12A1**

*On 21 FEB 2017 during the filling of Epinephrine Injection 0.3mg, Lot 7GM163, an operator reached over exposed sterile barrels.*

**OBSERVATION 12A2**

*Your sterile operators introduce sterile barrels to the Epinephrine filling in an area with no barrier protection and completely open to the surrounding room, classified as Grade B. In addition, your smoke studies demonstrated turbulence in this area.*

**Response to Observations 12A1 and 12A2**

During the inspection, an operator was observed using (b) (4) The observation was made at the TV monitor in SPM Corridor Room (b) (4) that was projecting an image from the video camera in APA Room (b) (4). From the visual perspective of the video camera as seen on the TV monitor, it appeared as though the Filling Technician's forearm was located directly above (b) (4) (sterile barrels). When interviewed, the subject technician stated her arm was not over the (b) (4) because she was aware that she should reach around the (b) (4) to avoid having her hand or forearm above the (b) (4). When viewed by an observer standing in Room (b) (4) and facing an operator performing this action, the hand or forearm does not go over the sterile (b) (4) when this action is performed properly.

An investigation (QAR PR 28567) was initiated regarding this observation. On 21MAR2017 as part of the investigation, to evaluate the possibility that the TV monitor was not spatially accurate or representative of the actual aseptic technique, we had a QA representative observe through the monitor the same operator who was observed by the investigator used the proper technique in the APA Room. On the monitor, the operator appeared to place her forearm over the sterile barrels, as the FDA Investigator observed, though in fact she had not. The investigation thus concluded that this operator performed the action properly in this case. However, the investigation also identified that the applicable site procedures do not provide sufficient detail on how to (b) (4) from the (b) (4). It also revealed that the (b) (4) Filler (b) (4) is not surrounded by a barrier to prevent movement above the (b) (4), which could in theory impact the sterility of the barrels used for filling as noted in Observation 12B2. Finally, the investigation showed that the (b) (4) used to remove (b) (4) are not designed to facilitate easy removal.

Personnel and environmental monitoring data for Room (b) (4) Grade A/B areas for 2015 through February 2017 are documented in the tables below. This data demonstrates no impact to the

environmental state of control of the line or quality of products despite the issues identified in the investigation.

| Sample | Year | Number of Action Level Excursions | Total Number of Samples | Action Level Excursion % |
|---|---|---|---|---|
| Personnel | 2015 | 96 | (b) (4) | (b) (4) |
| | 2016 | 135 | | |
| | Jan/Feb 2017 | 38 | | |
| Room (b) (4) Grade A | 2015 | 2 | | |
| | 2016 | 4 | | |
| | Jan/Feb 2017 | 1 | | |
| Room (b) (4) Grade B | 2015 | 0 | | |
| | 2016 | 0 | | |
| | Jan/Feb 2017 | 0 | | |
| Room (b) (4) Passive Air (b) (4) (Near (b) (4) (b) (4) ) | 2015 | 0 | | |
| | 2016 | 0 | | |
| | Jan/Feb 2017 | 0 | | |

In Response to the Observations and the investigation we performed, the following corrective actions have or will be taken:

- On 08MAR2017, the subject Filling Technician successfully participated in a media fill and performed the (b) (4) activities which were previously observed. The subsequent media-filled units showed no signs of growth.
- A barrier will be installed on the (b) (4) Filler to protect the (b) (4). The barrier in this area of the filling process will enhance HEPA filtered airflow and reduce potential for human intervention during the (b) (4). This new barrier will be implemented by 15JUN2017. Smoke study and media fill will be performed as part of the barrier installation project's comprehensive validation.
- Awareness training will be performed to reaffirm all (b) (4) filling technicians' understanding of the required aseptic technique for (b) (4) from the (b) (4) Filler (b) (4). This activity will be covered by all (b) (4) and Filling Technicians and will take place prior to epinephrine filling production resumption on 30APR2017.
- Procedures, documentation, and training associated with the action of (b) (4) from the (b) (4) will be enhanced at the 15JUN2017 barrier implementation. Applicable site personnel will train on this documentation update and the action will be added to the aseptic training program.
- (b) (4) and/or specialized tools will be designed and implemented by the 15JUN2017 barrier installation. These tools will better facilitate the (b) (4) of the (b) (4) Filler.
- Methods for loading all components on the (b) (4) Filler line will be evaluated by the corporate Microbial and Aseptic Support group by 15JUN2017. An action plan for other (b) (4) Filler line enhancements will be developed by 01JUL2017 as needed based on the findings of the evaluation.

**OBSERVATION 12A3**

*During filling operations of ATNAA Lot 7M1131 on 21 FEB 2017, your operator made intervention with their torso over units on the ATNAA line in two instances.*

**Response to Observation 12A3**

Personnel working on the (b) (4) Filler (b) (4) Filler Machine are trained and qualified to perform aseptic interventions. As specified in SOP-PRO-FIL-00001, *General Aseptic Procedure*, the entire body should be kept out of the path of unidirectional airflow to the extent possible when performing interventions. For cases where there is no means to access an area without opening the barriers, interventions are defined and tested as part of the media fill program to ensure they are performed as intended and potential impact to the product is challenged.

The intervention observed during the inspection, intervention (b) (4) at (b) (4), is a defined intervention in SOP-PRO-FIL-10050, (b) (4) *Filler Aseptic Processing Events (Interventions and Activities) Recording and Actions,* (b) (4) *Filler - Room* (b) (4). At (b) (4), the previously (b) (4), from the (b) (4) assembly machine to the filling machine where they are (b) (4). Interventions in this area are associated with the removal of a (b) (4) located on the (b) (4)).

During the execution of intervention (b) (4) at (b) (4), the operator is expected to (b) (4) to access the (b) (4) from the (b) (4). Whenever this intervention is executed, because of the position of the (b) (4), the operator has to (b) (4) and temporarily position a part of their body over the (b) (4) where product units are located. There is currently no other available method to perform this action. Attempting to perform this intervention from a different location would result in the operator disrupting unidirectional airflow over sterile components, i.e. the (b) (4).

When the operator's torso does enter Grade A, no sterilized part is contacted by the operator and the fluid path is not manipulated (b) (4)). All (b) (4) once the (b) (4), per filler (b) (4) thus limiting the risk of contamination to product units.

Environmental Monitoring data for Room (b) (4) for 2015 through February 2017 year to date demonstrate that the area has been maintained in a state of control. Table below provides the environmental monitoring data for Room (b) (4).

| Sample | Year | Number of Action Level Excursions | Total Number of Samples | Action Level Excursion % |
|---|---|---|---|---|
| Personnel | 2015 | 96 | (b) (4) | (b) (4) |
| | 2016 | 135 | | |
| | JAN-FEB 2017 | 38 | | |
| Room (b) (4) Grade A (Active Air, Passive Air, Surface Samples) | 2015 | 0 | | |
| | 2016 | 1 | | |
| | JAN-FEB 2017 | 0 | | |
| Room (b) (4) Grade B (Active Air, Passive Air, Surface Samples) | 2015 | 1 | | |
| | 2016 | 0 | | |
| | JAN-FEB 2017 | 0 | | |
| Room (b) (4) Passive Air (b) (4) (Closest sample location in proximity to intervention) | 2015 | 0 | | |
| | 2016 | 0 | | |
| | JAN-FEB 2017 | 0 | | |

As shown in the table above, there was only 1 action level excursion each in Grade A and Grade B in this period. There were no action level excursions at sample location (b) (4) the sample location in closest proximity to intervention (b) (4).

In addition, interventions associated with (b) (4) were successfully challenged (b) (4) times during media fills in the past 3 years, all with acceptable results.

| Media Fill Protocol No. | Media Fill Execution Date | Number of Times Intervention #31 Executed | Media Fill Results |
|---|---|---|---|
| QP 13-811 | Oct-13 | 3 | Pass |
| QP 14-808 | Apr-14 | 1 | Pass |
| PR10072 | Nov-14 | 7 | Pass |
| PR15008 | May-15 | 4 | Pass |
| PR18181 | Oct-15 | 8 | Pass |
| PR17707 | Dec-15 | 4 | Pass |
| PR17709 | Jan-16 | 4 | Pass |
| PR19689 | Jan-16 | 13 | Pass |
| PR22717 | Aug-16 | 1 | Pass |
| PR25310 | Nov-16 | 7 | Pass |
| PR24738 | Jan-17 | 5 | Pass |

MMT will engage SME's within Industry network with expertise in the design of aseptic equipment barriers to evaluate whether modifications can be made to the (b) (4) Filler, e.g. (b) (4), to reduce the risk of contamination during intervention (b) (4) and all other interventions performed on the (b) (4) Filler. This evaluation will be completed by 31DEC2017. Based on the conclusions of the evaluation, an action plan will be developed by 31JAN2018 to implement equipment modifications or other recommendations made by the expert.

**OBSERVATIONS 12B**

*Regarding your media fill program:*

**OBSERVATIONS 12B1**

*For ATNAA, an operation that requires* (b) (4) *, the number of units were* (b) (4) *as seen in the table below. The media fill for the Epinephrine line is* (b) (4) *.*

| *Product* | *Target Fill* | *Media Fill* | *Media Fill* | *Media Fill* |
|---|---|---|---|---|
| *ATNAA* | (b) (4) *units* | (b) (4) *units* *06 JAN 2017* | (b) (4) *units* *11 NOV 2016* | (b) (4) *units* *21 DEC 2015* |
| *Epinephrine* | (b) (4) *units* | (b) (4) *units* *05 JAN 2017* | (b) (4) *units* *18 NOV 2016* | (b) (4) *units* *22 JAN 2015* |

**OBSERVATIONS 12B2**

*The number of media fills is not commensurate with the* (b) (4) *. Although your firm operates* (b) (4) *, only* (b) (4) *media fills are required* (b) (4) *for both the Epinephrine and ATNAA lines. Your firm uses an approach* (b) (4) *and is* (b) (4)

**Response to Observations 12B1 and 12B2**

The current media fill program includes a robust demonstration of interventions that are representative of the number, type and complexity of normal interventions that occur in each run as well as non-routine interventions. Each major and minor intervention must be performed (b) (4) and the total number of major and minor interventions must (b) (4) on the production batch record.

The current requirement of not less than (b) (4) units per media fill in SOP-QLA-VAL-00020, *Media Challenge of Aseptic Processes*, was based on the (b) (4) units starting point recommended in FDA's Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice.

MMT would like to clarify that SOP-QLA-VAL-00020, *Media Challenge of Aseptic Processes*, requires a media fill to be performed (b) (4) frequency in accordance with FDA's Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. The 2 year history table below details the media fills for the ATNAA/DuoDote (b) (4) Filler) and Epinephrine (b) (4) Filler) fill lines and demonstrates that we have met or exceeded the semi-annual requirement.

**2 Year Media Fill History**

| Equipment Name and Location | Filling Date | Duration of Fill | Protocol Number | # of Units Incubated | # of Units w/ Growth |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

*Terminated or invalidated media fills addressed in Response 12B3.

Following the acquisition and qualification of (b) (4), SOP-QLA-VAL-00020 will be revised by 31OCT2017 to require each semi-annual media fill to produce a minimum of (b) (4), for a required minimum total of (b) (4) units per media fill (b) (4) media fill on (b) (4) which will be performed at (b) (4) to qualify the allowed fill duration at a worst-case.

Performance of number of interventions at NLT (b) (4) (NLT (b) (4)) filled units will qualify intervention action limits at a worst-case. A table describing limits for interventions that are implemented during production and during media fill as well as new media fill intervention requirement associated with (b) (4) unit media fill can be found below.

| Product | Intervention Type | # of Interventions Defined and Noted in Batch Record | Batch Record Intervention Limit | Past Media Fill Intervention Requirement | New Media Fill Intervention Requirement[1] |
|---|---|---|---|---|---|
| Epinephrine | Major | (b) (4) | NMT (b) (4) per (b) (4) units | NLT (b) (4) | NLT (b) (4) |
| | Minor | | NMT (b) (4) per (b) (4) units | NLT (b) (4) per (b) (4) units | NLT (b) (4) per (b) (4) units |
| ATNAA / DuoDote | Major | | NMT (b) (4) per (b) (4) units | NLT (b) (4) | NLT (b) (4) |
| | Minor | | NMT (b) (4) per (b) (4) units | NLT (b) (4) per (b) (4) units | NLT (b) (4) per (b) (4) units |

[1] Associated with the new requirement for (b) (4) units

**OBSERVATION 12B3**

*Your firm aborted (b) (4) media fill batches for ATNAA without the clear justification as required by procedure SOP-QLA-VAL-00020 Media Challenge of Aseptic Processes which states in part, "*** A media fill run shall be aborted (invalidated) only under circumstances in which written procedures require (b) (4) . Supporting data and justification shall documented [sic] in such cases***". Your firm had no production procedures that specified the conditions that were used to justify invalidate (b) (4) media fill batches on the (b) (4) (ATNAA) line.*

**Response to Observations 12B3**

MMT would like to clarify that deviations to the manufacturing processes are handled under the *Event and Deviation Reporting (ER & QAR)* procedure (SOP-QLA-MQA-00720) and the lot impact is assessed by QA. QA was consulted before the (b) (4) media fill batches were aborted, per procedure, and all integral filled units were incubated and no growth was observed.

The reasons for invalidating/terminating (b) (4) media fills on the (b) (4) Machine and the actions taken in response to these events are summarized below:

- Media Fill PR 5582 (performed in 2014): The (b) (4) Machine was unable to meet the protocol requirements for minimum filling duration, minimum fill speed, minimum of (b) (4) good filled units incubated and minimum number of minor interventions. An investigation concluded the protocol requirements were not met due to equipment malfunction that caused downtime. The media fill was invalidated as less than the amount of units required by the protocol was produced. All integral filled units (including good filled units, (b) (4) samples and (b) (4) samples, (b) (4) , (b) (4) and (b) (4) rejects) were incubated and no growth was observed. Additionally, growth promotion was acceptable. The investigation identified corrective actions to correct and prevent the equipment malfunctions. The media fill was successfully repeated.

- Media Fill PR 13397: During the execution of the media fill an operator mistakenly (b) (4) and the filling line was immediately stopped. An investigation concluded that the root cause was Human Performance. The media fill was terminated as less than the amount of units required by the protocol was produced. All integral filled units (including good filled units, (b) (4) samples and (b) (4) samples, (b) (4), (b) (4), and (b) (4) rejects) were incubated and no growth was observed. Additionally, growth promotion was acceptable. The investigation determined that this was an isolated incident and preventive action was not required. The media fill was successfully repeated.

- Media Fill PR 17708: During the execution of the media fill, reoccurring fault codes led to extended periods of downtime ((b) (4)) in which the machine was unable to produce integral units. The root cause was determined to be equipment/electrical failure. The media fill was terminated due to the inability to operate the filling machine and was not considered representative of a normal production batch. All integral filled units (including good filled units, (b) (4) samples and (b) (4) samples, (b) (4), (b) (4), and (b) (4) rejects) were incubated and no growth was observed. Additionally, growth promotion was acceptable. Corrective action was taken to address the equipment/electrical failure. The media fill was successfully repeated.

A new production procedure will be created by 29SEP2017 to include examples in which production lots would be aborted, such as machine inoperability requiring extensive maintenance work, break in asepsis, and non-sterile components running on the line.

**OBSERVATIONS 13**

*Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance. Specifically,*

**OBSERVATIONS 13A**

*Epinephrine, as stated in the appropriate master batch records, is required to be (b) (4), however, controls within the inspection and assembly area ((b) (4)) are deficient since:*

**OBSERVATIONS 13A1**

*Units were observed in the inspection and assembly area being (b) (4) and were not (b) (4) during breaks.*

**OBSERVATIONS 13A2**

*Your firm is not currently calculating the (b) (4) during all phases of production nor are you currently comparing the (b) (4) against a specified criteria.*

**OBSERVATIONS 13A3**

*Your firm has not measured the impact of* (b) (4) *) and the* (b) (4) *in the inspection and assembly area from:*

*i.* (b) (4) *used as* (b) (4) *as part of the* (b) (4) *process for the* (b) (4) *in* (b) (4)
*ii.* (b) (4) *used as* (b) (4) *as part of the* (b) (4) *in* (b) (4) *in* (b) (4)
*iii.* (b) (4) *from* (b) (4) *in* (b) (4)
*iv.* (b) (4) *of* (b) (4) *that is used as* (b) (4) *in order to aid in the inspection at the* (b) (4)
*v.* (b) (4) *from* (b) (4) *from* (b) (4) *in* (b) (4)
*vi.* (b) (4) *from* (b) (4) *in* (b) (4) *in* (b) (4)

***Response to Observations 13A1, 13A2 and 13A3***

Stability data for EpiPen and EpiPen Jr. units (b) (4) supports that these products are stable through expiry. The manufacturing process with respect to (b) (4) for the EpiPen products has not changed since the inception of the Next Generation auto-injector (NGA) in 2009 and implementation of the (b) (4) inspection systems in 2008. During the manufacturing process, all units are (b) (4) which include the (b) (4) system and (b) (4). Currently, formulation/filling batch records at the Brentwood site contain statements that the (b) (4). Assembly/Inspection/Packaging Batch records at the Westport site contain the statements that the product is (b) (4) basic units when not processing.

Published literature cites (b) (4) is in the family of compounds that can be classified as (b) (4) is monitored as part of the EpiPen stability program. In reviewing EpiPen and EpiPen Jr. stability data from 2012 through 2017, all results for (b) (4) are "None Detected" and all results for (b) (4) conformed to specification. These two results support a lack of significant (b) (4). Of these stability lots, EpiPen lot 5GN341 was processed through the (b) (4) systems (b) (4) and (b) (4) through the manual inspection process. Lot 5GN341 also met specification for (b) (4) and (b) (4) through expiry. The stability data supports that the current process controls which (b) (4) are acceptable.

In order to assess the worst case (b) (4) during production, a (b) (4) study will be performed. The study will include measurement of (b) (4) at all product (b) (4) at both the Brentwood and Westport facilities, including at the (b) (4) systems. During the study a group of test units and control units (b) (4) across the entire manufacturing process. (b) (4) will represent worse case conditions. Results from the test and control units

will be compared to determine if any additional process (b) (4) controls should be implemented. The (b) (4) study will be completed by 30JUN2017.

As an additional precaution and pending results from the (b) (4) study, current instructions on (b) (4) will be clarified to include when and how units should be protected, e.g., ensuring all totes containing product are (b) (4). SOP-MAN-INS-10154, *Single Chamber Auto-Injector Basic Unit Inspection,* and Reference Manuals RM-MAN-INS-10153, RM-MAN-INS-10152 and RM-MAN-PKG-10159 will be updated to include these instructions by 15MAY2017.

**OBSERVATION 13A4**

*Your firm is not currently evaluating the potential impact of epinephrine (b) (4) as part of the overall investigation process.*

1. *Based upon review of production data, Epinephrine Batch 6GM059 had been inspected (b) (4) in (b) (4) ( (b) (4) ) and therefore (b) (4) (all units were (b) (4) and the (b) (4) ). This batch was subsequently released by the firm; and during commercial distribution received a complaint related to Liquids Atypical Color / Cloudy. The subsequent compliant investigation (MMT Complaint Number 2016-07-0037004-US) did not consider the atypical nature of the inspection process nor the potential (b) (4) as a root cause factor.*

***Response to Observation 13A4***

Stability data for EpiPen and EpiPen Jr. units (b) (4) conditions supports that these products are stable through expiry. Published literature cites (b) (4) which are (b) (4) In reviewing EpiPen and EpiPen Jr. stability data from 2012 through 2017, all results for (b) (4) were "None Detected" and all results for (b) (4) conformed to specification. Of these stability lots, EpiPen lot 5GN341 was processed (b) (4) and (b) (4) through the manual inspection process. Lot 5GN341 also met specification for (b) (4) through expiry. The stability data supports that the current process controls which (b) (4) are acceptable.

Complaint report 2016-07-0037004-US was for EpiPen units from lot 6GM059 that appeared "brown" when held up or against a paper and "clear" when held up to light. Upon receipt of the complaint, (b) (4) reserve samples were inspected for discoloration from lots 6GM059 and 6GM060, the only other lot that was filled from the same bulk formulation lot as 6GM059. There were no discolored units. The investigation also determined there were no other related complaints for lot 6GM059 and that there was also no product trend for cloudy/discolored complaints. The investigation included a review of quality investigations (for lot 6GM059 and for similar events for the product) and concluded none were related to the complaint and that there was also no related product investigation trend. The investigation included a review of the batch record, in-process inspections, and product release testing.

Subsequently, two un-activated complaint samples from lot 6GM059 were returned. The units were disassembled and evaluated and both units contained a clear and colorless solution which conforms to the product appearance specification. The complaint was not confirmed by either the initial investigation or the updates to the investigation following receipt of the returned samples.

A similar complaint for "brown" solution was reported but not confirmed for lot 6GM060 which was filled from the same bulk formulation lot.

A review of 5 years of data determined there have been no confirmed complaints for discolored/cloudy EpiPen or any observations of discolored/cloudy EpiPen during any inspection of reserve samples.

SOP-QLC-QLE-00702, *Product Complaint Handling*, and SOP-QLA-MQA-00720, *Event and Deviation Reporting (ER & QAR)*, will be revised by 31MAY2017 to include an instruction that the potential impact of reprocessing or atypical environmental conditions, such as (b) (4) be considered during relevant investigations.

**OBSERVATION 13B**

*SOP-QLA-GEN-00802, version 10.0, Management of Changes for Equipment, Facilities and Manufacturing Processes, Effective Date: 23 MAR2016" fails to require documentation of effectiveness checks for completed change controls. Process validations are completed* (b) (4) *but are not evaluated or trended to determine impact to the overall manufacturing process; additionally, complete process validations for autoinjector manufacturing processes such as EpiPen and ATNAA/DuoDote have not been revalidated since the initial validations. Risk assessments are not required to be performed for every change. The aforementioned procedure does not define criteria or provide examples indicating when risk assessments are necessary to be completed for the change.*

**Response to Observation 13B**

**Change Control:**

Per SOP-QLA-GEN-00800, *Management of Changes*, all changes that require a change management record are, at minimum, assessed for regulatory, quality, and environmental, health, and safety impact and are documented as part of the change approval process. Change management records also identify the activities required to support the implementation of the change. The impact assessment may determine, where appropriate, that a risk assessment should be conducted or modified in support of or as a result of a major change.

Effectiveness checks are performed through performance and/or process validation and are required for all major process changes. Additionally, change effectiveness is checked as part of the associated investigation process in the event that an incident occurs after the implementation of a change per the current version of SOP-QLA-GEN-00802, *Management of Changes for Equipment, Facilities and Manufacturing Processes.*

SOP-QLA-GEN-00802 will be revised by 31AUG2017, to define requirements and provide examples for when to perform change effectiveness checks and risk assessments, specifically, for post-market design changes to combination products.

**Process Validation:**

MMT would like to clarify that process validations have been performed for EpiPen and ATNAA/DuoDote since the initial process validations (PV). The PVs performed have included those parts of the process that were potentially impacted by process changes.

For example in the EpiPen process:

- A process change to increase the EpiPen bulk formulation batch size was performed in 2007. The PV for this process change was performed under QP 07-108 and the bulk formulations were used in conjunction with the filling and assembly process to generate EpiPen auto-injectors for stability studies conducted under RP-514. MMT has not made significant changes to the formulation process since this activity that would warrant revalidation of the formulation process.
- A process change to EpiPen filling was performed with the installation of a new (b) (4) in 2010. The PV for this process change was performed under QP 10-110 which covered the filling, (b) (4) inspection, assembly, and final product inspection. MMT has not made significant changes to the filling and assembly process since this activity that would warrant revalidation of the process.
- A process change to the EpiPen automated inspection machine was implemented in 2016. The PV for this process change was performed under PR 20990/PR 21016 which covered the automated inspection process. In addition, the inspection results of the PV were evaluated against inspection results of (b) (4) production batches prior to the change and (b) (4) production batches after the conclusion of the PV. MMT has not made significant changes to the automated inspection process since this activity that would warrant revalidation of the process.

For example in the ATNAA/DuoDote process:

- A process change to increase the Pralidoxime Chloride bulk formulation batch size was implemented in 2008. The PV for this process change was implemented under QP 08-103, QP 08-118, and QP 08-123. MMT has not made significant changes to the formulation process since this activity that would warrant revalidation of the formulation process.
- A process change to the ATNAA/DuoDote filling was performed with software changes to the (b) (4) Filler in 2014. The PV for this process change was performed under PR 8955/ PR 8957 which covered the filling, (b) (4) ), manual inspection, assembly, and final product inspection. In addition, the manual inspection results of the PV were evaluated against historical PV manual inspection results to demonstrate the effectiveness of the change in reduction of critical defects. MMT has not implemented significant changes to the filling and assembly process since this activity that would warrant revalidation of the process.

The Annual Product Records Review (APRR) process includes verifying the consistency of the process, confirming whether product consistently met specifications and limits, identification of significant trends, and identification of any corrective or preventive actions based on the reviews. Summaries of both change management records and qualifications and validations are included in the APRR. All data and information in the APRR is evaluated for any significant trends.

To establish a current baseline of the complete manufacturing processes for EpiPen and ATNAA/DuoDote, as recommended, full process validations from formulation through labeling of the assembled unit will be completed by 15DEC2017 for EpiPen and 29JUN2018 for ATNAA/DuoDote.

**OBSERVATION 14**

*Employees engaged in the manufacture, processing, packing and holding of a drug product lack the training required to perform their assigned functions. Specifically, your firm did not conduct training for employees involved in the visual inspection for* (b) (4) *used in EpiPen manufacturing. For example, your Site Lead reported there is no formal OJT for the visual* (b) (4) *evaluation (inspection) before the* (b) (4) *is introduced into the process. There are no job aides to assist operators in identifying defects and there are no visual examples of defects in the procedure. There is also not a defined time frame that the* (b) (4) *" must be evaluated for the following defects:* (b) (4) *. The evaluation of the* (b) (4) *is not timed. The operators are not qualified for visual acuity or accuracy in discovering defects for this inspection before performing the* (b) (4) *evaluation task.*

**Response to Observation 14**

All (b) (4) lots received at MMT are subject to incoming quality control testing per Quality Control Test Report 4013004. This incoming acceptance testing includes visual inspection for defects and dimensional specifications. Colleagues that perform incoming acceptance testing for (b) (4) reference RM-QLC-SQC-10555, Defect Reference Manual for the (b) (4) Component. The reference manual includes photos, defect classifications, definitions, and descriptions of (b) (4) defects. Per a review of training records, all colleagues who perform this activity have completed training for RM-QLC-SQC-10555.

Evaluation of the (b) (4) during the (b) (4) in the Clean and Prep area is governed by SOP-PRO-CLP-00005, (b) (4) *Evaluation at* (b) (4) (b) (4). This procedure describes the process for (b) (4) evaluation during a pre-use preparation step that is conducted prior to (b) (4) and subsequent filling operations. This evaluation is not an inspection of individual units to assure end product quality, but rather a pre-use step that is performed to improve the downstream manufacturing step process flow and yields. As such, all of the controls that apply to the inspection of individual product units (e.g., visual acuity testing, evaluation time duration, etc.) do not apply to the pre-use evaluation of (b) (4). Any defects found during the pre-use evaluation are rejected from the lot. Per a review of training records, all colleagues who perform this activity have completed training for SOP-PRO-CLP-00005.

After units are filled, all finished basic units undergo (b) (4) separate 100% inspections which include the rejection of individual units with potential (b) (4) defects. The (b) (4) separate 100% inspections are:

(b) (4)

Inspectors that perform (b) (4) and MVI of finished basic units are qualified per SOP-MAN-INS-00029, *100% Manual Inspection Qualification*. Qualification requires (b) (4) and (b) (4) testing. Qualification also requires the successful inspection of qualification test kits containing acceptable units and defects, with (b) (4) and (b) (4) (b) (4) thereafter. Per a review of training records, all inspectors who perform (b) (4)-(b) (4) or MVI of finished units have completed training requirements per SOP-MAN-INS-00029.

To further improve the process robustness for the pre-use evaluation of (b) (4) during the execution of SOP-PRO-CLP-00005, the following improvements will be made to procedures and the training process:

- A job aid which includes visual examples and further details for the steps performed during the pre-use evaluation of (b) (4) will be created by 07JUN2017.
- A new On-The-Job (OJT) training document will be developed and implemented by 07JUN2017 for all colleagues that perform pre-use evaluation of (b) (4). The new OJT will require review of the job aid, review of SOP-PRO-CLP-00005, and hands on training.